"REPURPOSING OF MIRTAZAPINE FOR THE MANAGEMENT OF ORPHAN DISEASE- PROGRESSIVE MULTIFOCAL LEUCOENCEPHALOPATHY (PML)"

&

"QUALITY OF LIFE ASSESSMENT OF ORAL CANCER PATIENTS AFTER MANDIBULAR RESECTIONS USING UWQOL (V4) QUESTIONNAIRE: RECONSTRUCTION WITH PECTORALIS MAJOR MYOCUTANEOUS FLAP"

A Thesis Submitted to

NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

CLINICAL PHARMACY

BY

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May 2015

CERTIFICATE

This is to certify that the dissertation work entitled "Repurposing of Drug for the Management of Orphan Disease- Progressive Multifocal Leucoencephalopathy (Pml)" submitted by Ms. Drasty Sanjaybhai Vora with Roll No. (13MPH703) in partial fulfillment for the award of Master of Pharmacy in "Clinical Pharmacy" is a bonafide research work carried out by the candidate at the Department of Pharmacology, Institute of Pharmacy, Nirma University and at QED Clinical services PVT LTD under our guidance. This work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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DECLARATION

I hereby declare that the dissertation entitled "Repurposing of Drug for the management of Orphan Disease- Progressive Multifocal Leucoencephalopathy (PML)" is based on the original work carried out by me under the guidance of Dr. Jigna S. Shah, Professor and Head, Department of Pharmacology, Institute of Pharmacy, Nirma University and Mr. Ali Sajjad Bohra, Regional Head, QED Clinical Services. I also affirm that this work is original and has not been submitted in part or full for any other degree or diploma to this or any other university or institution.

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We wish her success in all future Endeavors.

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List of Contents

Part-1

ABBREVIATIONS

PART-II	
AML	Acute Myeloid Leukemia
BBB	Blood Brain Barrier
CNS	Central Nervous System
CSF	Cerebrospinal Fluid
FLAIR	Fluid Attenuated Inversion Recovery
JCV	John-Cunninghum Virus
MRI	Magnetic Resonance Imaging
PML	Progressive Multifocal Leucoencephalopathy
QSAR	Quantitative structure-activity and relationships
R & D	Research and Development
US and EU	United States and Europe
PART –II	
EORTC	European Organisation for Research and Treatment of Cancer
HNC	Head and Neck Cancer
HRQOL	Health Related Quality of Life
IFN	Interferon
IGFBP	Insulin-like growth factor-binding protein
MMP-3	Matrix Metalloproteinase-3
PMMF	Pectoralis Major Myocutaneous Flap
UW-QOL	University of Washington Quality of Life

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CHAPTER-1 ABSTRACT

ABSTRACT

Introduction

Orphan diseases are the ones which affect fewer numbers of patients. The definition of orphan diseases varies from country to country. As per USA, An orphan disease is defined as a condition that affects fewer than 200,000 people nationwide. The major challenges associated with orphan drug development are less number of affected patients, high cost, unknown aetiology of diseases, limited information etc. Hence, taking the very fact into consideration, a new field that has come into existence is **Drug Repositioning/Repurposing. By definition, Drug repositioning (also known as Drug repurposing, Drug re-profiling, Therapeutic switching and Drug re-tasking) is the application of known drugs and compounds to new indications (i.e., new diseases).** Progressive Multifocal Leucoencephalopathy is a serious brain disorder caused by JC Virus. It is an orphan disease having very less number of patients. The aim of this study is to carry out thorough literature search and to find drug regimen for the treatment of PML.

Objectives:

- To review already existing drugs for their suitability for the treatment of Progressive Multifocal Leucoencephalopathy.
- Identify one potential medication for Orphan designation in PML.

Search Strategy:

A complete meta-analysis was carried out and drugs already used for PML were searched along with proposed drug for the treatment. Suitable proofs were collected to show its efficacy and among them a drug with best outcomes and strong evidences was taken for further investigation.

Results:

Many drugs were screened but due to lack of proper evidences they were not taken for further studies.Among them Mirtazapine showed positive outcomes in case reports. It completely cures infection of the initial stages. Mirtazapine has been used as an off label treatment for management of progressive multifocal Leucoencephalopathy. Many case reports showed positive outcomes of Mirtazapine and the virus infection gets fully cured at the initial stages of the infection. Mirtazapine also shows promising results when used in combination therapy. Thus Mirtazapine was further investigated and a clinical trial design of Mirtazapine was proposed as till date no clinical trial has been conducted on Mirtazapine for the management of PML.

Conclusions:

IL-7 and Imatinib are drugs already orphan designated for the treatment of PML, but they are associated with some toxicity. Based on the evidences available Mirtazapine showed a positive ray of hope for the treatment of PML and can be repurposed and designated for PML. We hope that the trial design can be taken up by some company and Mirtazapine gets an orphan drug designation for Progressive Multifocal Leucoencephalopathy in near future.

Key words:

Mirtazapine, Progressive Multifocal Leucoencephalopathy.

CHAPTER-2 INTRODUCTION

INTRODUCTION

Orphan diseases/rare diseases are the ones which affect fewer numbers of patients. The definition of orphan diseases varies from country to country. As per USA, An orphan disease is defined as a condition that affects fewer than 200,000 people nationwide.[1] It is important to note that 80% of rare diseases have identified genetic origins whilst others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative.[2] 50% of rare diseases touch/affect children.[3]

Orphan disease is defined in different aspects globally as follows:

Country	Orphan Disease definition
U.S	A drug developed under the Orphan Drug Act, January 1983 is an orphan drug in US market. A disease that affects fewer than 200,000 people or is of low prevalence (less than 5 per 10,000 in the community) is termed as an Orphan Disease in US.
Europe	A disease or disorder that affects fewer than 5 in 10,000 citizens.
Japan	Any disease with fewer than 50,000 prevalent cases (0.4%).
Australia	Any disease orconditions affecting fewer than 2,000 individuals at any one time is termed as orphan disease in Australia.
Canada	Canada has no official “orphan disease” status; however, based on international standards, it could be defined as diseases with a potential patient population around 3,300.
Asian Perspective of Rare Disease	
India	The need for an orphan act is evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would strengthen the infrastructure of health services and provide relief to numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by Indian Drugs Manufactures Association in 2001 requested Indian Government to implement

	Orphan Drug Act in India.
Taiwan	The official definition of rare disorders is a disease if it is prevalent in 1:10,000 people. On February 9, 2000, Taiwan's Legislative Yuan implemented the Rare Disease and Orphan Drug Act to improve the diagnosis, treatment, and prevention of rare diseases in Taiwan.
Korea	If less than 20,000 people are affected from any disease or if there is no treatment available for that disease, than it is termed as Rare/Orphan disease in Korea.

Table 2.1 Definition of Orphan Disease globally

An Overview of Drug Discovery Process:-

Drug discovery has always been an interesting field with multiple challenges yet with rewarding and satisfying outcomes. A typical drug discovery process would take around 10-15 years of time to bring a new drug to the market; and consumes around 1 billion US dollars or sometimes even more specially with biologicals and specialty medicines. However, the successes of the drugs developed are not guaranteed. It is estimated that 90% of all drugs entering various clinical trials are discontinued, more often due to issues associated with efficacy than safety.

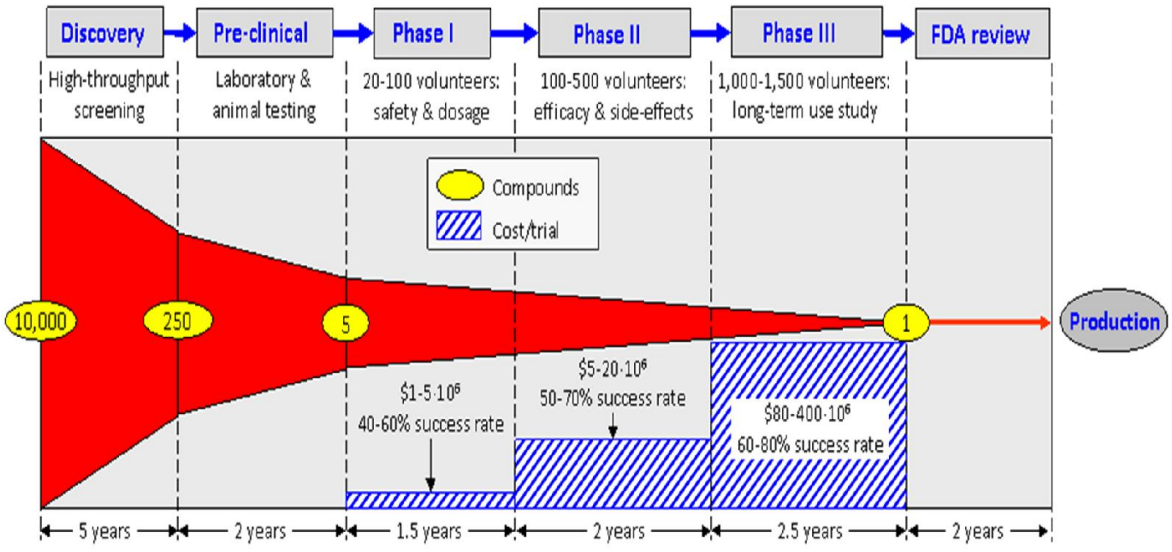


Fig: - 2.1 overview of Traditional drug development process

Drug development process in orphan diseases is generally slow due to limited information available on the disease and scarcity of the patients and also due to several other operational and cost factors. Also there are over 7000 rare diseases known in this world. The clinical development and designation for these rare diseases drugs is far different compared to traditional diseases and their drugs as shown in figure below. The major challenges associated with orphan drug development are less number of affected patients, high cost, unknown aetiology of diseases, limited information etc. Thus orphan drug development is really a challenging and very difficult task.

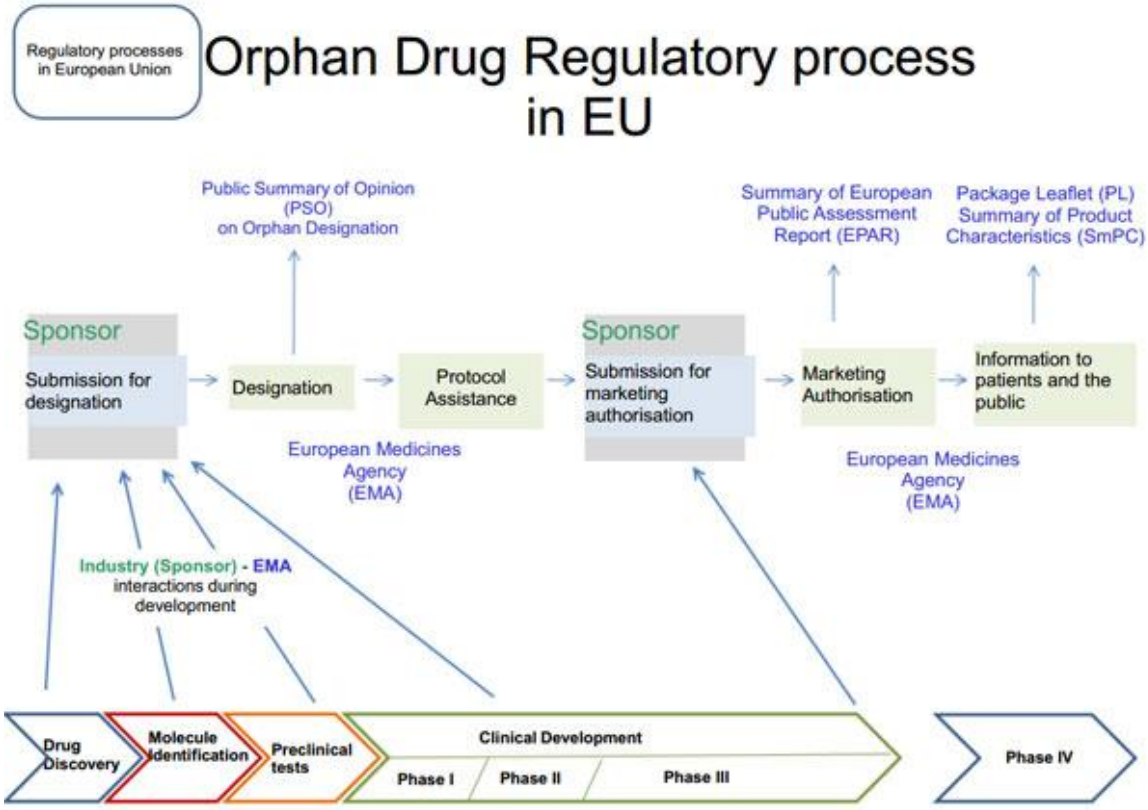


Fig: -2.2 An overview of Orphan drug development and designation process.

Taking the very fact into consideration, a new field that has come into existence is **Drug Repositioning/Repurposing. By definition, Drug repositioning (also known as Drug**

repurposing, Drug re-profiling, Therapeutic switching and Drug re-tasking) is the application of known drugs and compounds to new indications (i.e., new diseases). [4]

Drug repurposing offers to explore the existing knowledge on drugs, diseases and targets and helps us to find a novel use of an already available compound or drug lead for the development of new and better therapies. Since drug repurposing offers a relatively low-risk, recovering losses, save both money and time, most companies are now heading for reprofiling of existing drugs. It is because of this reason drug reprofiling is becoming increasingly popular in the industry. A few older instance of drug repurposing are like **Sildenafil**, a generic drug, initially used for Angina was later repositioned and used for Erectile Dysfunction and Pulmonary Hypertension. **Aspirin** was originally meant for treating pain, is now prescribed as a vasodilator for reducing the risk of heart attack and strokes. **Minoxidil**, a generic drug made for hypertension and manufactured by Pharmacia & Upjohn in Sweden was repositioned by Pfizer for Rogaine, the drug's trade name, currently used for the treatment of hair loss.

Repurposing efforts in orphan disease areas can also prove to be very valuable in bringing newer medication to rare disease patients who are in desperate need of medications for the management of their diseases.

Table:-2.2 Examples of some Repositioned Drugs in various diseases are as follows: - [5]

Drug	Original Indication	New Indication
Aspirin	Inflammation, pain	Anti-platelet
Bromocriptine	Parkinson's Disease	Diabetes Mellitus
Finasteride	Prostate Hyperplasia	Hair loss
Gemcitabine	Viral Infection	Cancer
Methotrexate	Cancer	Psoriasis, Rheumatoid Arthritis
Minoxidil	Hypertension	Hair loss

Raloxifene	Cancer	Osteoporosis
Thalidomide	Morning Sickness	Leprosy, Multiple Myeloma

Similarly, Examples of Repositioned Drugs for **Orphan disease** is as follows:-

Table 2.3 Examples of Repositioned drugs in Orphan Diseases

Drug	Original Indication	Orphan Indication
Ciprofloxacin	Anti-infective	Cystic Fibrosis
Mifepristone	Abortifacient.	Hypercortisolism
Miltefosine	Antifungal and Antiprotozoal	Cutaneous T-cell Lymphoma
Ascorbic acid	Scurvy	Charcot-Marie-Tooth disease type 1A
Ketoconazole	Anti-infective	Treatment of Cushing syndrome
Sialic acid	Acne	Treatment of hereditary inclusion body myopathy
Amphotericin B	Fungal Infection	Leishmaniasis

Various methods utilised for Drug Repositioning are as follows:-

1) Drug Focus Approach: - Structural features of molecules already approved for particular indications can help to identify active compounds that were originally developed for different indications. Advanced software's can perform similarity searches and produce advanced QSAR models based on the collections of bioactive compounds in the world including compounds from patents and articles registered in databases, and other

sources. Drug Focus approach can be done by two ways "On-target" and "Off-target". In "on-target" approach, drug's pharmacological mechanism is already known that will be applied to the new indication. It can be possible that same mechanism of drug can treat other several diseases (Pfizer's Sildenafil having mechanism of vasodilation but it was unsuccessful in hypertension but it was successfully used in male erectile dysfunction and by applying same mechanism it was designated for pulmonary arterial hypertension a rare disease) and "off-target" means looking or identifying a newer mechanism of existing molecule and approaching it. It is more innovative approach for drug repurposing. A molecule is taken and extensive literature search is carried out for its published work and all possible mechanism will be identified and then after identifying newer possible mechanism and specific targets screening will be done and result will be narrow down to a limit till a molecule can be effective in targeting certain type of diseases. Off target approach requires more time for drug repurposing as new possible mechanism is to be identified. An existing molecule is already been used for a particular disease so complete data of a molecule will be available.

2) Disease Focus:-Experimental data related to disease or knowledge on how drugs modulate phenotypes related to disease (e.g. Known from their side effects) are checked in disease focus approach. An orphan disease with unknown pathophysiology, aetiology and unmet medical need will be approached and existing drugs will be targeted for that disease and effectiveness of drug will be checked for that particular disease.

Orphan drug development benefits:

In past, Pharmaceutical companies had very limited interest in orphan drug development due to heavy investments and limited returns. To promote research in orphan areas, health agencies have brought some unique advantages which have attracted biopharmaceutical companies to start working in the orphan drug areas.

In our thesis we are targeting repositioning of drug in an orphan disease named Progressive Multifocal Leucoencephalopathy, therefore it is important to know that for the orphan drug development health agencies has come up with many benefits which are listed as below:-

- Designation is granted based on prevalence of disease in the population of less than 200,000 people (approximately 0.1%) and 5 in 10,000.
- Protocol assistance to design research protocols.
- Funding grants for clinical research to support development.
- Tax credits for clinical research.
- Market exclusivity.
- Orphan drug market exclusivity of different countries is as follows:-

Countries	**Market Exclusivity**
US	7 years
Europe	10 years
Japan	10 years
Korea	6 years
Singapore	10 years
Taiwan	10 years

Table:-2.4 Orphan Drug Market Exclusivity of Different Countries

Rationale

There are various reasons for utilising drug repositioning/repurposing efforts for orphan diseases. Few of the logical reasons are as follows:

- There are over 7000 orphan diseases out of which only 300-400 have established medications for treatment. Hence, there is an unmet medical need to develop drugs for the management of orphan diseases.
- Traditional drug development approaches would take over 500 years to find treatment for all these diseases.
- Global slowdown, drying pipelines, increased R&D costs, expiring patents of block-buster drugs and cost pressure deters pharma companies to invest large sums for the development of orphan drugs.
- Repurposing/Repositioning of existing drugs with known pharmacology/toxicology for the treatment of orphan diseases is most appropriate, less time consuming and cost effective approach.

Keeping the above mentioned facts in mind, we planned to study the repurposing of drug for the orphan disease progressive multifocal Leucoencephalopathy.

Aim:

Repurposing/Repositioning the drugs for the management of orphan disease-Progressive Multifocal Leucoencephalopathy (PML)

Objectives:

- Review already existing drugs for their suitability for the treatment of Progressive Multifocal Leucoencephalopathy.
- Identify one potential medication for Orphan designation in PML.

CHAPTER-3

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Progressive Multifocal Leucoencephalopathy (PML)

PML is a rare infection of CNS that damages the white matter of the brain[7]. PML is the inflammation of the white matter of the brain at multiple locations. It is a rare infection which damages the Myelin Sheath that covers and protects Nerves in the white matter of the brain[8]. Although it is a rare disease but serious infection may lead to severe disability or death.[9]

PML is caused by a virus known as JC virus (John cunninghgum Virus-named from the initials of the patient from whose tissues the virus was first successfully cultured)

Majority of the adult Population is infected with the JC virus but do not develop the disorder. The virus activates only in certain conditions such as weakened immune system or due to certain immunosuppressant drugs.[8]

PML is a rare disorder, but it can occur in a various types of patients such as follows:-

- AIDS and HIV patients
- Cancer patients such as Lymphoma and Leukaemia
- Chronic steroid therapy to suppress Immune system.
- Transplantation of organs
- Immunosuppressive conditions.
- Certain therapeutic treatments affecting the immune system such as medicines used to prevent organ transplant rejection, or to treat Multiple Sclerosis, Rheumatoid Arthritis, PML is aggravated as their side-effects.[7]

Symptoms of PML are as follows: -

- Loss of co-ordination.
- Loss of language ability
- Seizures
- Memory loss
- Vision Problems
- Weakness of the legs and arms

- Personality changes
- Headaches[8]

Symptoms typical of PML are the result of demyelination – often in multiple areas of the brain – caused by the viral infection. Symptoms vary and increase in severity as disease progresses. PML frequently presents as hemiparesis, ataxia, cognitive or behavioural changes, or visual disturbances. It is important to note that diagnostic criteria should be considered in the context of primary indications and therapeutic areas. Neither fever nor optic nerve involvement is a feature of PML, and spinal cord disease is rarely associated with it. Symptoms begin gradually and usually worsen progressively and severe disability or death may often result.

Symptoms may differ depending on the part of the brain affected.

If PML is left unmanaged, the mortality rate is 30-50% within the first three months of diagnosis.

Even if death does not result, it is likely that some significant damage will be permanent.[8]

Risk Factors: -

PML is likely caused by a combination of factors. Risk factors include the presence of pathogenic JCV and an altered or weakened immune system; they may also include genetic or environmental risk factors.

1. Presence of Pathogenic JC Virus.

   Mostly Majority of the adult population is likely to be infected with JCV, only the presence of altered virus is seen in PML patients. Thus presence of altered virus having mutations in the non-coding region or the VP1 envelop protein is considered as a risk factor for PML. ELISA Test enables us to detect anti-JCV antibodies indicating past infection. This assay can be used in patients to identify the higher risk for PML in patients because of JCV infection. However, it cannot distinguish between antibody against wild-type and mutated virus. Other methods to detect JCV infection may not be sufficient because of poor sensitivity (assays

for JCV DNA in blood) or intermittent (viremia or) viruria (assays for viral DNA).[9]

2. Weakened Immune System

Compromised immune system enables infection and viral replication in the brain which is one of the key risk factors for PML. Aggravating factors which alters immune system and resulting in PML is as follows:-

- HIV-AIDS
- Lympho reticular malignancies
  - Chronic Lymphocytic Leukaemia
  - Hodgkin's disease
  - Non-Hodgkin's Lymphoma
- Systemic Lupus Erythematosus
- Treatment with certain immunosuppressive or immunomodulatory therapies in the context of:
  - Crohn's disease
  - Multiple Sclerosis
  - Oncology
  - Psoriasis
  - Rheumatoid Arthritis
  - Transplantation

Also some drugs aggravates PML as a part of their side effects. The list of such drugs is as follows:-

- Rituximab
- Natalizumab
- Alemtuzumab
- Cyclophosmamide
- Prednisolone
- Mycofenolate mofetil

- Tacrolimus
- Dexamethasone[10]

3. Genetic Risk Factors

Naturally occurring JCV sequence variation, together with drug treatment-induced cellular changes, may synergize to create an environment leading to an increased risk of PML.

The rarity of PML in the general population suggests that additional factors may contribute to susceptibility in conjunction with viral mutation and immune suppression/modulation. It has been proposed that certain human genetic or environmental risk factors may increase susceptibility to PML; however, specific risk factors have not yet been identified.[11]

Diagnosis of PML is mainly done by two methods as follows:-

1. Brain Imaging Characteristic of PML.(MRI)

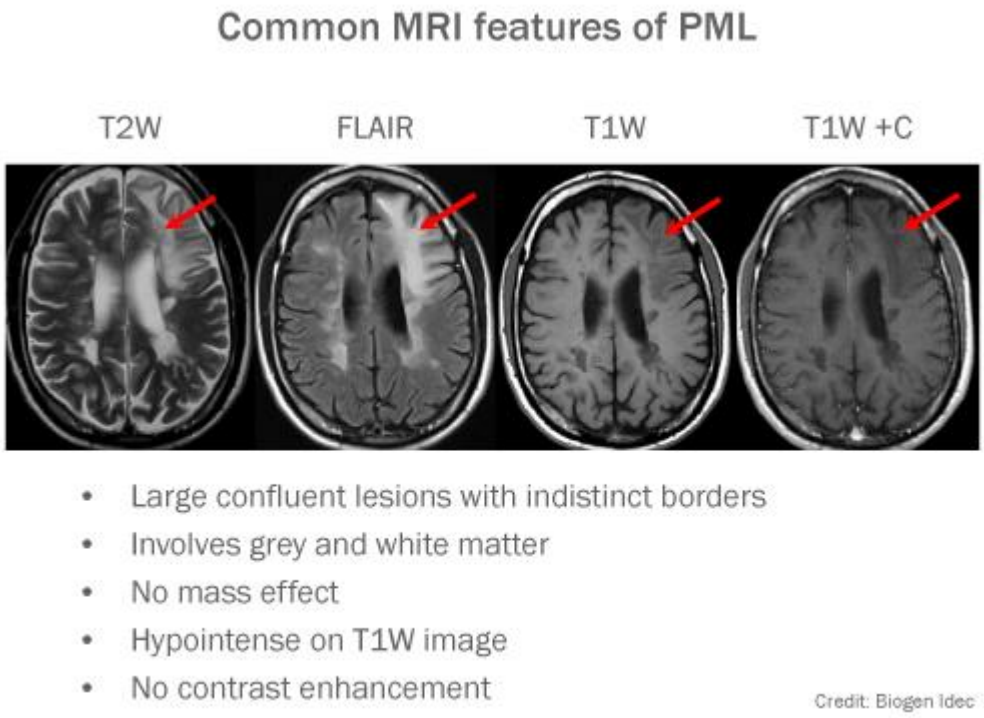
   Magnetic Resonance Imaging method is the mostly used and reliable technique to evaluate neurological status and progression of brain lesion.

Table: - 3.1 Brain Imaging characteristic of PML

Conditions	Explanation of Symptoms	Technique for Detection
Brain Imaging Characteristics	Unifocal or Multifocal Lesions	MRI

PML is associated with Unifocal or multifocal lesions, which may be detected using MRI. The lesions most commonly appear in the subcortical white matter or cerebellar hemispheres and are hyper intense on T2-weighted images and/or FLAIR (fluid-attenuated inversion recovery) sequences, and hypo intense on T1-weighted images.

In rare cases, the presentation of PML may be a progressive cerebellar disease, in which case an MRI would only display cerebellar atrophy, or a cortical presentation; for this reason, clinical vigilance is crucial to the early identification of PML-related signs and symptoms.[11]



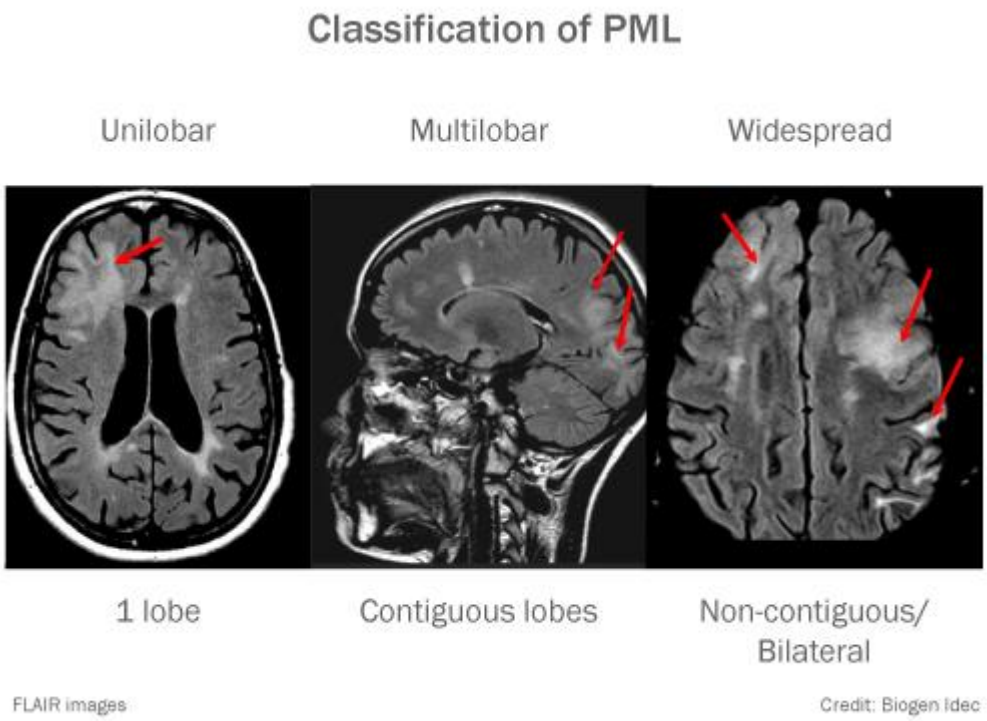


Figure 3.1 Features and Classification of PML

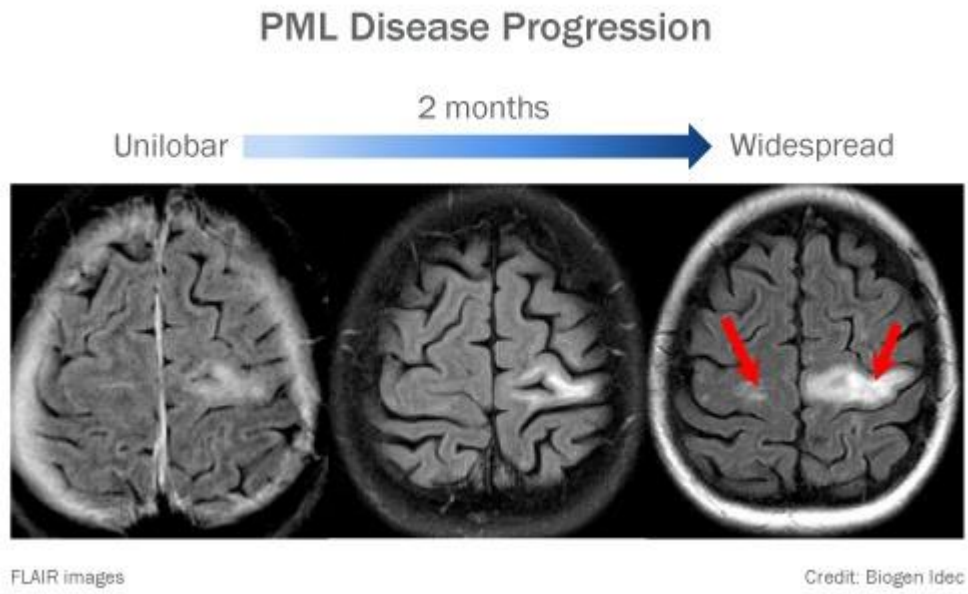


Figure:-3.2 PML Disease Progression pattern

2. Detection of JC virus DNA in the Cerebrospinal Fluid or Evidence of JCV Infection on a Brain Biopsy.

Finding of JCV DNA in brain biopsy is considered as a final diagnosis of PML. JCV DNA is not detectable in the early stages of the disease and additional biopsy should be done. Also expertise in JCV detection is needed due to the complexity by virus mutations. Highly sensitive and quantitative PCR test is suggested.[12,13]

Incidence and Prevalence of PML

As such no proper data were available regarding the prevalence of PML extensive literature search was carried out.

Methodology for finding prevalence of PML: - literature search was carried out by putting Mesh term "Progressive Multifocal Leucoencephalopathy"; search was carried out from PubMed, Science Direct, specific journal of different countries and search engine Google. Total of 3271 articles were screened out from PubMed from 1960-2014.[14-61]

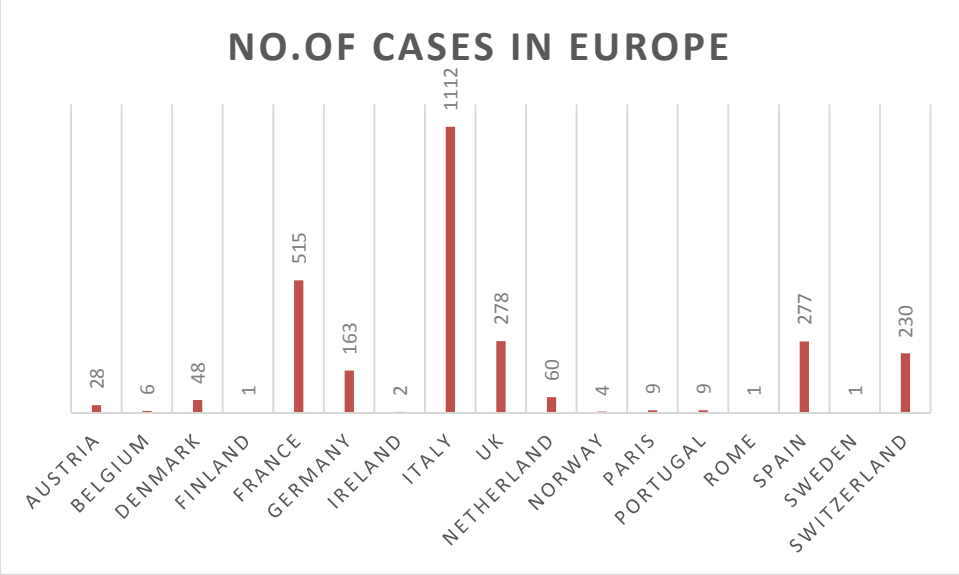


Figure:-3.3 Prevalence of PML in Europe

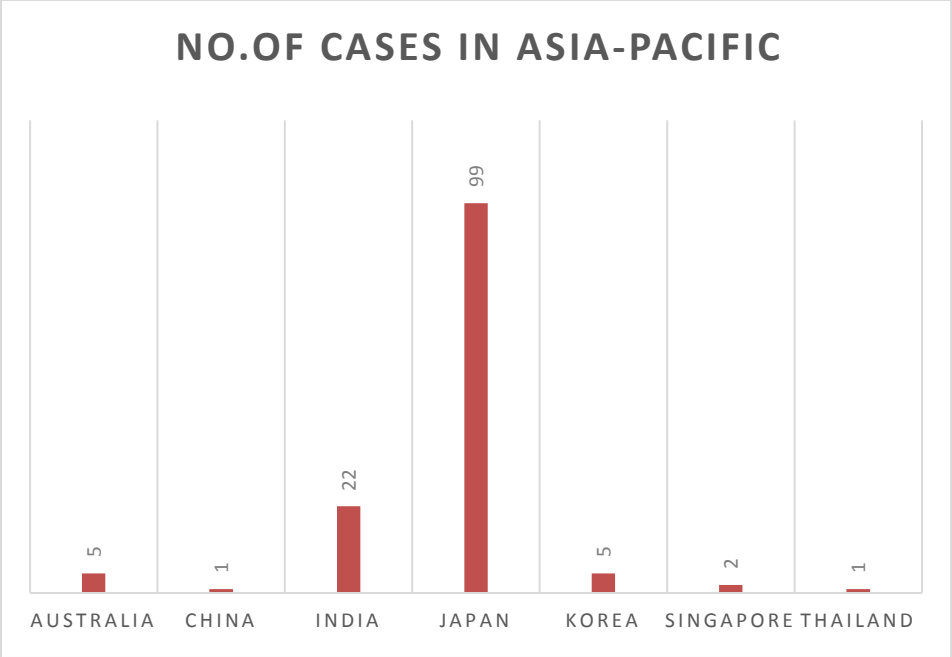


Figure:-3.4 Prevalence of PML in Asia-Pacific

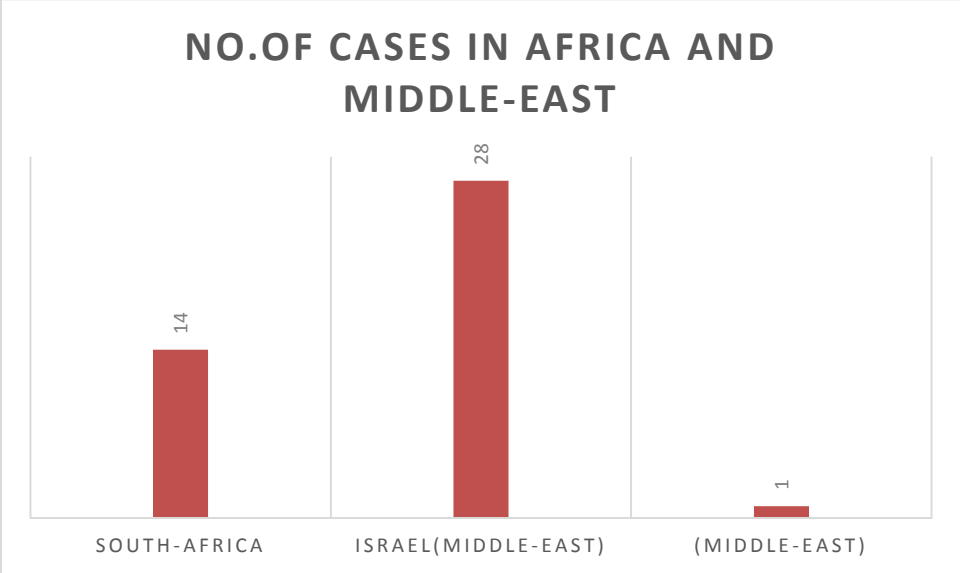


Figure:-3.5 Prevalence of PML in Africa and Middle -East

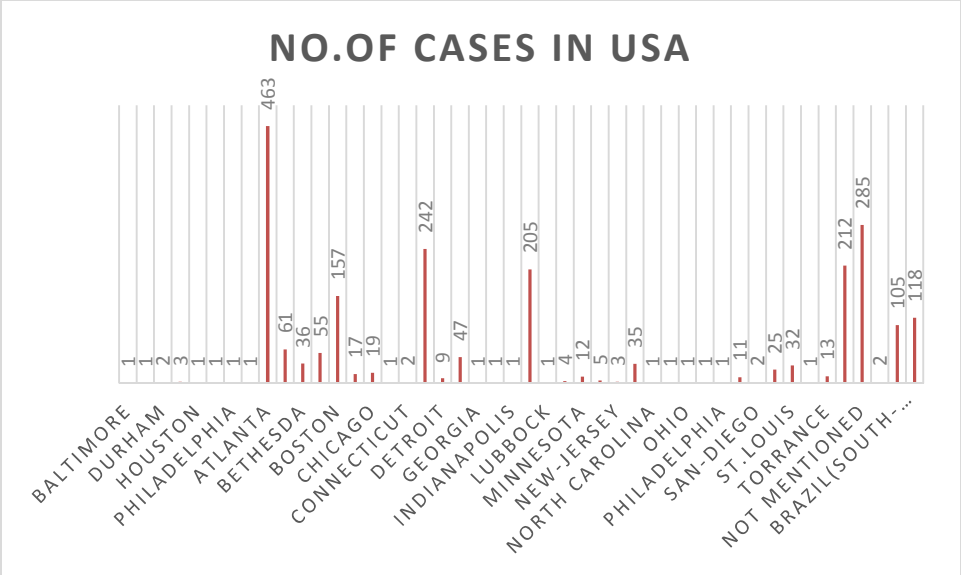


Figure:-3.6 Prevalence of PML in USA

The total number of cases was found to be 4899. U.S and Europe was found to have the highest number of PML cases.

Mechanism/Pathogenesis of PML.

JC Virus selectively targets cells in the kidney and brain. JCV requires sialic acids to attach to host cells and initiate infection, and JCV demonstrates specificity for the oligosaccharide lacto series tetra saccharide c (LSTc) with an α2,6-linked sialic acid. Following viral attachment, JCPyV entry is facilitated by the 5-hydroxytryptamine (5-HT) $_2$ family of serotonin receptors via clathrin-dependent endocytosis. JCPyV then undergoes retrograde transport to the endoplasmic reticulum (ER) where viral disassembly begins and infection occurs.[62,63]

Treatment:-

There is no convincing treatment for PML till date. Many anti-viral therapies such as cidofovir and mefloquine have been tried for the management of PML. However, the results were not encouraging. Various mechanisms have been studied by the scientists to fight against PML such as:-

1) Drugs stimulating the immune system (interleukin-2, Alpha Interferon and Beta Interferon)

2) Drugs that block viral entry into cells (chlorpromazine, Risperdone, mirtazapine) and

3) Drugs that target the replication of the virus (cidofovir, CMX001, mefloquine, Cytarabine and Topotecan).

Imatinib and IL-7 is an orphan designated drug for the treatment of PML.

CHAPTER-4

METHODOLOGY

SEARCH STRATEGY

Figure:-4.1 the search strategy process, we followed to target a drug regimen for PML is as follows:-

Methodology in detail:-

1. Drug screening and to find possible mechanisms

   Various drugs used in the treatment of PML is assessed and evaluated for its efficacy for the treatment of PML on the basis of case reports and data available by extensive literature search.

2. Data support and Data mining

   After completing extensive literature search and target screening, number of evidence will be found for that particular approach. The strength of evidence will provide main benefit of approaching drug for PML. This can be done by more literature search, combining and interpreting all available data.

3. Expert opinion

   For drug repurposing, the expert's opinion will be considered as an important factor. Expert opinion will be taken from research scholars, principle investigators of different clinical trials.

4. Commercial benefit and Scientific interest

   Drug repurposing is mainly carried out to treat disease with unmet medical needs in a cost effective approach. As new drug discovery requires lot of investment, commercial benefit will be found from the incidence of the disease. Additionally country like U.S. gives medical re-imbursement for particular diseases. So, that will provide more benefit to the pharma-companies and to the patients also. Scientific interest will be found from the strength of evidence of work for the particular drug (if you are working on disease driven approach than the evidence of work done on that disease and different mechanism of drug on that disease therapy)

5. Clinical trial design/ clinical trial outlook and Applying for orphan drug designation in EU/US market

Lat step in drug repurposing is clinical trial design. Clinical Trial is designed with the help of primary and secondary endpoints related to drug, its dose and effectiveness. After that, clinical trial should be carried out to confirm the effect of the drug in the particular disease. After trial and proofed results, drug can be applied further for orphan designation.

Proposed treatment for PML

Thus to target PML two approaches were taken into consideration from the mechanism as follows:-

1) To inhibit or bind sialic acid to hinder attachment of virus with the host cells.

2) To target entry of virus using 5HT2 Antagonist.

Proposed Drugs

1. **Lectins**

Certain plant lectins such as a lectin from the seeds of Maackia amurensis binds sialic acid and inhibits cell growth and migration.Mistletoe lectin (viscumin) binds proteins containing α2, 3-sialic acid, has undergone successful clinical trials, and is widely used to treat melanoma in Europe. High sialic acid leads to cancer as it creates negative charge on cell membranes which creates repulsion between cells and thus produces cancer. These lectins are widely used to treat cancer.

These Lectins can be used for treating PML as it hinders sialic acid thus the virus will not find sialic acid and infection will not initiate.[64]

2. **Sialic acids analogs**

Selective strategies to interfere with sialic acid synthesis might offer a good approach to treat progressive multifocal Leucoencephalopathy.

Also P-3F (ax)-Neu5Ac is a fluorinated sialic acid analog and blocks the synthesis of sialic acid by depleting alpha 2, 3 and alpha 2, 6 linked sialic acids. [65]

3. Oseltamivir and Zanamivir

Anti-influenza drugs like oseltamivir and Zanamivir are sialic acid analogs that interferes with the release of newly generated viruses by cleavage of sialic acids. Thus these drugs can also be used for treating PML.

4. Gallic acid

Several compounds were screened to check the structure of JC viruses and it was reported that Gallic acid possesses similar chemical space as sialic acid to bind the JC virus. Even Gallic acid possesses good blood brain barrier crossing capacity.[66]

The efficacy of above mentioned compounds such as various lectins, Oseltamivir and Zanamivir were assessed by thorough literature study and following end results were seen

Table:-4.1 Compounds screened and their drawbacks

Name of compounds	Drawbacks
Lectins from Maackia Amurensis and Mistletoe Lectins.	PML has affinity for Alpha 2, 6-linked sialic acids whereas these lectins have affinities for Alpha 2, 3 -linked sialic acids. Thus not applicable in PML.
P-3F(ax)-Neu5Ac - a fluorinated sialic acid	Unknown compound and no full proof evidences available
Oseltamivir and Zanamivir	Cannot cross BBB so not applicable for PML
Gallic acid analogs and Terguride	Unknown compound and no related information available.(Evidences were not available for Terguride)

Thus due to above discrepancies the concept of targeting sialic acids will not work so another approach is taken into account.

5. Terguride

Terguride was also a proposed drug and could be targetted for PML due to the following reasons:-

- Terguride acts as 5HT2 A/ B Antagonist and can cross blood brain barrier.
- Terguride elevates dopamine levels which improves mood related disorders and results in euphoria or ecstasy.
- Terguride is orphan designated drug for pulmonary arterial hypertension and Systemic Sclerosis.
- Also it is very old molecule so toxicity and other data's such as teratogenicity etc. are available and is comparatively safe.
- Drug designated for treatment of PML IL-7 is associated with Renal and Ocular Toxicity, but terguride has tolerable side-effects such as Confusional state and Hyponatremia. Thus Terguride can be used as a possible ray of hope for the treatment of PML.

From Mechanism point of view Terguride can be employed for the treatment of PML, but clinical evidences and proof of using Terguride in PML is not available.

Due to lack of sufficient evidences Terguride cannot be suggested for further work because without evidence confirmation about the proposed mechanism does not hold any value. Thus Terguride is not studied further for Progressive Multifocal Leucoencephalopathy.

Reports and literature search have suggested use of 5-HT_2A receptor antagonists for the treatment of Progressive Multifocal Leucoencephalopathy. Also offline many serotonin antagonist drugs such as Mirtazapine, Risperdone, Olanzapine has been used and improvement in disease is reported. In certain case reports disease is cured completely.

5-HT_2 Receptors allows entry of virus So if 5-HT_2 receptor is blocked it will stop the further progression of disease.

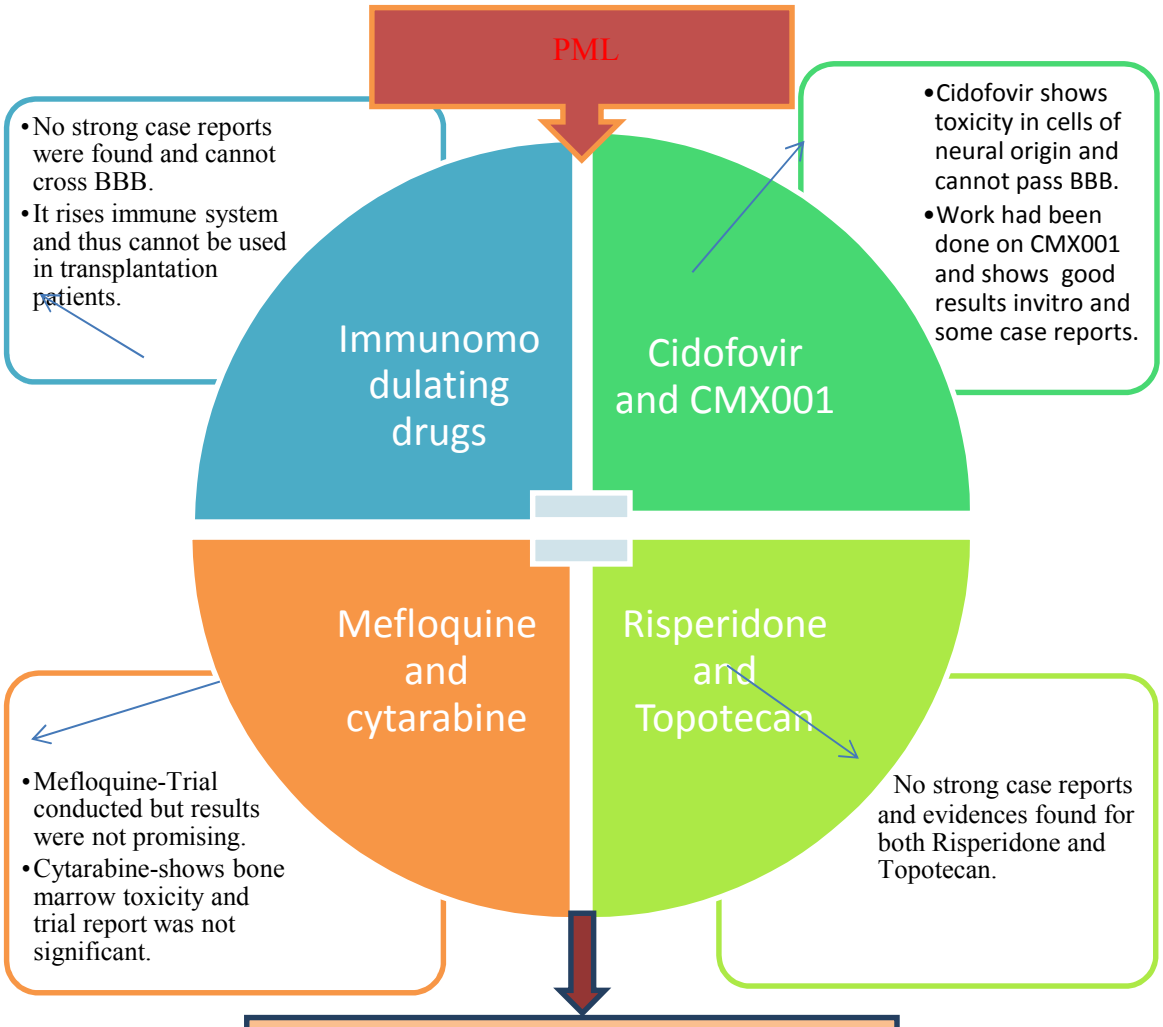
Below mentioned drugs are used offline for the management of PML and are scrutinized from pubmed articles.

Sr. no	Title	Name of Drug	No. of cases	Reference
1	Mefloquine improved progressive multifocal Leukoencephalopathy in a patient with immunoglobulin A nephropathy.	Mefloquine	1	J Clin Neurosci. 2014 Oct; 21 (10):1661-4. Doi: 10.1016/j.jocn.2013.12.031. Epub 2014 May 27.
3	Progressive Multifocal Leukoencephalopathy with Immune Reconstitution Inflammatory Syndrome (PML-IRIS): two case reports of successful treatment with Mefloquine and a review of the literature.	Mefloquine	2	Ann Acad Med Singapore. 2012 Dec; 41 (12):620-4.
4	Favourable outcome of progressive multifocal Leukoencephalopathy with Mefloquine treatment in combination with antiretroviral therapy in an HIV-infected patient.	Mefloquine	1	Int J STD AIDS. 2012 Aug; 23 (8):603-5. Doi: 10.1258/ijsa.2012.011305.
5	Neuropharmacokinetic heterogeneity of Mefloquine	Mefloquine	1	Intern Med. 2012; 51(16):2257; author reply 2259. Epub 2012

	in the treatment of progressive multifocal Leukoencephalopathy.			Aug 15.
7	Mefloquine improved progressive multifocal Leukoencephalopathy in a patient with systemic lupus erythematosus.	Mefloquine	1	Intern Med. 2012; 51(10):1245-7. Epub 2012 May 15
8	Pharmacokinetic considerations in the repositioning of Mefloquine for treatment of progressive multifocal Leukoencephalopathy.	Mefloquine	1	Clin Neurol Neurosurg. 2012 Oct; 114(8):1204-5. Doi: 10.1016/j.clineuro.2012.02.046. Epub 2012 Mar 14.
10	Akinetic mutism caused by HIV-associated progressive multifocal Leucoencephalopathy was successfully treated with Mefloquine: a serial multimodal MRI Study.	Mefloquine	1	Intern Med. 2012; 51(2):205-9. Epub 2012 Jan 15.
12	Mefloquine treatment in a patient suffering from progressive multifocal Leucoencephalopathy after umbilical cord blood transplant.	Mefloquine	1	Intern Med. 2010; 49(22):2509-13. Epub 2010 Nov 15.

13	Mefloquine in the treatment of progressive multifocal Leucoencephalopathy	Mefloquine	1	J Neurol Neurosurg Psychiatry. 2011 Apr; 82(4):452-5. Doi: 10.1136/jnnp.2009.190652. Epub 2010 Jun 20.
17	Treatment schedules for 5-$HT2_A$ blocking in progressive multifocal Leucoencephalopathy using Risperidone or Ziprasidone.	Risperidone and Ziprasidone	2	Bone Marrow Transplant. 2007 Jun; 39(12):811-2. Epub 2007 Apr 23.
18	Risperidone-induced reduction in JC viruria as a surrogate marker for efficacy against progressive multifocal Leucoencephalopathy and haemorrhagic cystitis.	Risperidone	1	J Clin Virol. 2007 May; 39(1):63-4. Epub 2007 Apr 3
20	The atypical antipsychotic agent's Ziprasidone [correction of Ziprasidone], Risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal Leukoencephalopathy.	Ziprasidone, Risperidone and Olanzapine	1	Med Hypotheses. 2005; 65(3):585-6.

Table:-3.3 list of drugs used offline for PML is as follows:-



WHY MIRTAZAPINE????

Because…..

- It shows promising results in case reports and combination therapy.
- Have strong evidences in disease improvement.
- Less explored.
- No clinical trial has been conducted so far for mirtazapine.
- No serious toxicities were associated with mirtazapine.
- Thus, we concluded to study Mirtazapine for further investigation.

Figure:-4.2 Presentation for why Mirtazapine is selected as a drug of choice

Screening of Individual Drugs:-

1. **Immunomodulating drugs**

   Interleukin-II, an Immunomodulating drug is responsible for the activation of Lymphocytes and is used in the treatment of specific forms of cancer. Three case reports of HIV patients along with PML showed positive responses when treated with IL-II. Other Immunomodulating drugs are Interferon alpha and beta. They interfere in replication of virus by activating macrophages and natural killer cells. A case control study in 1999 showed report on 53 HIV patients along with PML from which 21 were treated with Interferon alpha, showed increased survival of patients. Another study conducted in 2001 having 97 HIV patients from which 36 were treated with INF-alpha, showed no remarkable advantage over non-treated patients. One single case-study was found in which the patient having HIV was treated for four months with INF-beta but Brain lesions showed no significant improvement and patient died within four months. Thus Immunomodulating drugs are not much efficacious in PML as they lack BBB crossing capacity.[67,68]

2. **Cidofovir**

   According to the case reports and clinical studies from 1995 to July 2000, use of cidofovir for PML was reviewed. Most case reports suggested use of cidofovir to be effective in the treatment of PML. Cidofovir can be the most reliable treatment option for PML in HIV infected patients who fail to improve with HAART. A case report of HIV patient treated with cidofovir for PML was reported. In 1998, a case was reported in which patient was having PML with HIV, where cidofovir in addition to HAART was given to the patient and also showed improvement in Brain lesions. In the following years 10 different case reports were reported, 7 patients among them showed response to the treatment. The three patients that did not respond to the treatment were reported in one article and were not HIV infected, two had chronic lymphatic leukaemia and one had multiple myeloma. 6 out of the 7 other patients were HIV infected, one had chronic lymphatic leukaemia. Moreover, for all three non-responsive patients the diagnoses was based on both MRI scans and the detection

of JCV DNA in the Cerebrospinal fluid by PCR. Nevertheless only one patient among three post mortem examination was performed and PML was detected. On top of those case reports, 6 case control studies were performed. In 2008 Di Luca et al. combined the results of these 8 case control studies in which AIDS-related PML patients received combination antiretroviral therapy with or without cidofovir. It was concluded that there was no remarkable change in PML related mortality. Moreover, cidofovir showed some toxicity in cells of neural origin. It was not clearly distinguished that improvement is seen because of cidofovir or due to HAART therapy in HIV patients. Cidofovir cannot cross BBB and thus its derivative was prepared for more efficacy and BBB crossing capacities. [69-83]

3. **CMX001**

Cidofovir showed positive results in PML and also its in-vitro activity on Polyoma virus were good enough. Thus further investigations on cidofovir were continued for enhanced BBB penetration, and a lipid conjugate of cidofovir was derived by Chimerix. Inc. which was named as Brincidovir. Also its Phase-II trial showed prevention of Cytomegalo Virus infection. Many clinical trials were completed which shows CMX001 to prevent Cytomegalovirus by Sponsor Chimerix-A North Carolina Based Company. A study was conducted which states that CMX001 suppresses JC virus replication in human fetal brain SVG cell cultures.

It also inhibits replication of Polyomavirus. One case report was published of Idiopathic CD4+ Lymphocytopenia patient was survived and responded well to the treatment.

It was effective in small doses, thus chances of side-effects seen were also less. CMX001 can also pass BBB, thus it is an effective drug for the treatment of PML.[84]

4. **Mefloquine**

Mefloquine has been used widely for prophylaxis and treatment of malaria. Mefloquine was found to inhibit JC virus replication in patients given Mefloquine for malaria. This activity showed the ability to inhibit infection with JCV strains. A case

report of a 54year old female patient with Sarcoidosis showed decrease in Brain Lesions. It was the first report of successful treatment of PML with mefloquine.

2000 Approved drugs were assessed for Anti JCV activity and various drugs were checked for Anti JCV action and also devoid of cellular toxicities. Only Mefloquine was reported to show high penetration in CNS. Also in vitro studies showed that mefloquine inhibits the viral infection rates of three different JCV isolates, JCV(Mad1), JCV(Mad4), and JCV(M1/SVEΔ), and does so in three different cell types, transformed human glial (SVG-A) cells, primary human fetal glial cells, and primary human astrocytes. Mefloquine Inhibits viral replication in cells after viral entry. Although no suitable Animal model is available literature review suggested that mefloquine could be an effective therapy for PML.

Ten case reports were assessed from 2010 to 2014 in which mefloquine was used as a treatment along with HAART. Out of them 2 patients responded to the therapy, however among these two patients, one patient of Germany with Idiopathic CD4+ lymphocytopenia and one Patient of Australia with Waldenström's macroglobulinaemia, but the treatment was started late i.e after 2months and 5 months respectively after onset of PML.

Because these were all single patients that were treated for PML it is impossible to say with certainty that the improvement was due to Mefloquine. Although these results, along with the in vitro results were promising. However, a larger clinical trial with a total of 37 patients in 2013 was terminated prematurely, because the Data Safety Committee predicted a small probability of showing a significant difference in the outcome of the different groups in this study. Until the termination of the study, no activity of Mefloquine was observed. However, the number of patients was very limited. Also the patients were having various comorbid diseases and thus their survival chances were also varying. These combined facts, would have put the result to be in suspect, even if the study had not been terminated.

Also expert opinions suggested that Mefloquine have toxicities which are long lasting and some are life-long. Thus it was not considered for further study for targetting PML.[85,86]

5. **Cytarabine**

Cytarabine is a chemotherapeutic agent used mainly as treatment for haematological malignancies such as acute myeloid Leukemia (AML) and Non Hodgkin lymphoma. It affects the duplication of DNA and can therefore be a candidate for PML treatment. Cytarabine can, however, cause severe side effects, especially immune suppression. Eight case reports have been published till date and four among them were HIV infected. Out of these 8 patients, 7 showed response to the treatment with Cytarabine. The patients that did not respond had chronic lymphatic Leukemia. However, a study with 4 HIV infected patients treated with cytosine arabinoside showed no effect of the treatment, all 4 patients died within 71 days after the start of the therapy. Moreover, two larger studies showed no effect of Cytarabine on patients suffering from PML.

In a multi-centre trial, 57 HIV patients with PML were randomly assigned to receive one of three treatments: antiretroviral therapy alone, antiretroviral therapy plus intravenous Cytarabine, or antiretroviral therapy plus intrathecal Cytarabine. At the time of the last analysis, 14 patients in each treatment group had died, and there were no significant differences in survival among the three groups. Thus Cytarabine administered either intravenously or intrathecal does not improve the prognosis of HIV-infected patients with progressive multifocal Leucoencephalopathy who are treated with the antiretroviral agents.

19 Non-AIDS patients with PML were treated with IV Cytosine Arabinoside 2mg/kg per day for 5 days. Out of them 7 patients showed improvement within 6 months. Thus cytosine arabinoside showed 36% (7 out of 19) improvement. Also significant bone marrow toxicity was associated with the treatment. Therefore, it is very difficult to draw any solid conclusions from these results. Other clinical trials also did not show significant increase of survival chances while treated with Cytarabine.[87,88]

6. Topotecan

Topotecan is a chemotherapeutic agent primarily used in the treatment of cancer. Topotecan inhibits topoisomerase I and thereby DNA replication. The administration of Topotecan via an implanted ventricular reservoir can overcome the inability of Topotecan to cross the BBB. One non controlled clinical trial with 11 HIV patients where Topotecan was used showed a possible effect of Topotecan on lesion size and survival time. It was seen that Survival time increased and only 3 patients were survived. [89]

7. 5-HT_2 Antagonist Drug -Risperidone

One more drug acting on serotonin receptors and was also suggested as a possible treatment of PML is the antipsychotic Risperidone. A case report of non-Hodgkin lymphoma patient responding to Risperidone was also reported.[90]

8. 5-HT_2 Antagonist Drug-Mirtazapine

Mirtazapine is an antidepressant which activates serotonin receptors in the brain and is able to cross the BBB. It has been suggested that JCV uses those serotonin receptors to infect the central nervous system, Therefore, mirtazapine can be a suitable drug in the treatment of PML. One case report, a polycythaemia Vera patient, and 4 HIV infected patients case series have been published, all with positive outcome. All 5 patients responded to the therapy. However no clinical trials have been reported for this drug. Apart from all the drugs Mirtazapine was studied for further investigation as Cidofovir, CMX001 were used for the treatment of PML but very less work was conducted on 5-HT_2 Antagonist drugs and also Mirtazapine shows good results in treatment of PML.[91,92]

Table:-4.3 Case Reports of Mirtazapine showing positive outcomes for PML treatment.

Srno	No. of case reports	Drug	Co-morbidity	Positive outcome(yes/no)
1	1	Mirtazapine	Polycythaemia Vera	Yes
2	4	Mirtazapine	HIV	Yes
3	1	Mirtazapine Plus Cidofovir	Sarcoidosis	Yes
4	3	Mirtazapine Plus Mefloquine	2 patients with Multiple sclerosis and 1 with HIV	Yes
5	1	Mirtazapine Plus Cytarabine	Dermatomyositis	Yes
	Total=10			

A case report of 63 year old polycythaemia patient was reported in which Mirtazapine showed efficacy and the patient was neurologically stable with resolution of cerebral lesion.

Also Mirtazapine showed efficacy in HIV infected PML patient in one case series. 15mg of Mirtazapine was given weekly to the patient for 6 months in 4 HIV patients. Among them 1 patient showed improvement in MRI and 3 patient showed improvement in neurological functions. Clinical improvement was seen in patient who received mirtazapine therapy closest to PML symptoms onset period. From these case series, we can conclude that Mirtazapine is safe, well tolerated and offers marked benefits as a treatment or prophylaxis of PML.

One more case report of 45 year old man with systemic sarcoidosis treated with combination therapy of cidofovir and Mirtazapine showed significant improvement. Thus mirtazapine shows good results when used in combination therapy for the treatment of PML.

A combination treatment of Mirtazapine and Mefloquine on 3 patients also showed positive outcomes.

Studies with combination therapy.

Several case reports where PML patients have been treated with combination of at least one of the above mentioned drugs have been reported. One patient with PML was treated with cidofovir in combination with chlorpromazine. Chlorpromazine is a drug that may be prescribed for symptoms, i.e to control vomiting and nausea, to manage psychotic disorders and as a complement in the treatment of tetanus. In vitro experiments show that Chlorpromazine, is able to inhibit viral spread when given in low doses with neutralizing anti-JCV antibodies. Most likely because chlorpromazine is able to inhibit clathrin-dependent endocytosis by inhibiting the disassembly of the clathrin at the plasma membrane as well as inhibiting receptor cycling there. Without the antibodies the same results can be obtained at higher doses. However, there are significant side effects at higher doses. Chlorpromazine might be able to cross the BBB. The chronic lymphatic Leukemia patient treated with chlorpromazine and cidofovir showed no response to the treatment.

Two reports of combination therapy with IL-2 have been published, one is along with cytarabine and another in combination with cidofovir. Response were seen on patients treated with Cytarabine and this patient had underwent autologous bone marrow transplant.

Four reports on the combination of cidofovir with cytarabine have been published, all patients responded to the treatment. One patient having chronic lymphatic leukemia, the other three were HIV infected. One report on the combination of cidofovir with mirtazapine has been published, the sarcoidosis patient responded to the treatment. Three reports on the combination of mefloquine with mirtazapine have been published, all the patients responded to the treatment. Two patients were suffering from multiple sclerosis and one was HIV infected.

Combination therapy of Cytarabine and mirtazapine has been published in one report, the Dermatomyositis patient responded to the treatment.

Two reports on the combination of Cytarabine and INF-α have been published, both patients responded to the therapy. One patients had Cröhn disease the other one sarcoidosis. One report on the combination of mefloquine, mirtazapine and cytarabine was published, response was not good enough in patient with chronic lymphatic leukemia. Most of reports show a responds of the patient to the different therapies.[93,94]

Outcome of combination Therapy:-

Combination therapy shows good results for the treatment of PML, but according to the expert opinions, orphan designations are given to single drug molecules only, combination drugs does not covers orphan designations. Thus although used offline combination drugs cannot be orphan designated.

CHAPTER-5

RESULTS

RESULTS

- To date there is no specific treatment for PML. Only few medications showed favorable results in certain case reports.
- Drugs such as IFN-α, cidofovir, cytarabine and mefloquine that was evaluated in clinical trials, showed no significant results.
- Cidofovir is not convincing against PML, most likely on the grounds that it can't pass the BBB. Then again, an enhanced cidofovir drug, CMX001, showed promising results *in-vitro* on cell lines, it can cross BBB and showed marked improvement according to the case reports.
- Mefloquine also showed encouraging results in both in-vitro and in-vivo studies but a clinical trial with 37 patients was terminated in light of the fact that impact of mefloquine was not measurable.
- Cytarabine is generally tried for numerous situation reports, a number of the patients reacted to the medication. Also in clinical trials, no huge impact was measurable.
- Immunomodulating drugs such as IL-2 shows fair results in certain case reports but, it is not tried in clinical trials.
- INF-α has been indicated but it does not showed marked improvement.
- A patient did not showed any improvement to the treatment of INF-β thus it was not studied further.
- Chlorpromazine has only one case report in which the patient did not showed any improvement to the treatment.
- A trial for topotecan was reported and 3 out of 11 patients showed improvement in brain lesion.
- Serotonin receptors antagonist drugs such as risperdone and mirtazapine showed quite good results in case reports.
- Additionally, mirtazapine showed even more promising results in the case reports where it is utilized in combination with different medications. But no clinical trial has been reported for these drugs. Many combination therapies have been used offline but none of them have been tried for clinical trial. Hence we cannot further study these combinations without proofed data and evidences.

CHAPTER-6

DISCUSSION

DISCUSSION

PML is demyelinating rare disease of the brain triggered by the JC virus (JCV), It has a serious impact on patients who experience the ill effects of it and even the death rate is high. Patients with very weak immune system are affected by this disease. Patients treated with Natalizumab as a treatment regimen for multiple sclerosis are at highest risk of PML. To date, there is no convincing treatment found to treat PML. Challenges in finding treatment for such disease lie in a scope of reasons. To begin with, there is no animal model as JC virus replication does not occurs in non-humans. Thus preclinical testing cannot be carried out to assess effect of any drug on PML. Another reason is PML is an orphan disease, hence a patient pool with similar background of medical history and disease are impossible to find for conduction of clinical trial. We cannot get large number of patient pool and due to this drug efficacy cannot be proved with less sample size. Also underlying causes of the disease will vary from patient to patient for e.g. immune system can be compromised due to multiple reasons such as different drugs like Natalizumab, rituximab, Efalizumab/Alemtuzumab or by disease such as HIV and even due to organ transplantation. The underlying cause and stage differs and due to this strong conclusions cannot be obtained in clinical trials.

Research done in context of PML is very limited as it is an orphan disease; very less research has been conducted on JC virus mechanism and replication process.

The treatment of PML becomes more complex as the targeted drug should have blood brain barrier crossing property. Cidofovir was effective invitro but as it does not penetrate BBB, it was failed in in-vivo studies. A derivative of cidofovir named CMX001 showed good results in case reports as it can cross BBB. Immunomodulating drugs cannot cross BBB and also they cannot be used in the treatment of PML in transplantation patient as they boost immunity which may result in rejection of the transplanted organ.

Drugs such as Mefloquine, Risperidone and Mirtazapine were able to cross BBB and also Mirtazapine was showing comparatively good outcomes. Thus we selected Mirtazapine for further study for the management of PML.

CHAPTER-7

CONCLUSION

CONCLUSION

From all the drugs reviewed it was assessed that CMX001, Mirtazapine and Risperidone were most encouraging. These drugs can cross Blood Brain Barrier, has no severe side effects and showed positive results in case reports and in *in-vitro* studies. However, none of these drugs have been tested in controlled clinical trials, so further research is needed for these drugs.

CMX001 is a patented drug. Based on all the available evidences, Mirtazapine was selected as a suitable drug treatment for PML and a clinical trial design for Mirtazapine was designed for further progress and research. A proposed trial design for Mirtazapine is as follows:-

Mirtazapine Trials Design

Title: - A Randomized Study to explore the effect of Mirtazapine in subjects with initial stage infection of PML.

Study Type: - Interventional

Study Phase: - Phase-III

Condition: - Progressive Multifocal Leucoencephalopathy(PML)

Intervention: - Drug: - Mirtazapine and Placebo

Dose: - 15 mg orally

Sample Size: - 36

Rational for Drug, Dose and Sample Size selection:-

As mentioned in previous sections of this thesis, Mirtazapine has been found to be useful in early stage of PML to reduce the JC virus load. This study is designed to evaluate the effect of Mirtazapine compared to Placebo for the early stage cases of PML.

The dose selected for this study is based on series of case reports published in reputed journals.

The sample size has been considered with respect to prevalence of disease (5 in 10,000) and previously conducted clinical trials.

Design:-Placebo control.

Treatment Duration: - 24 weeks

Identification techniques:-

MRI and detection of JCV in CSF and decreased levels of CD4+ (normal range 500-1500) and CD8+ (normal range 250-950 cells per mm^3) is used as a diagnostic tool to detect PML.

Viral load more than 1000 copies/ml are seen. (Normal range of viral load is less than500 copies/ml)

Symptoms of PML:-

- Loss of co-ordination.
- Loss of language ability
- Seizures and hemiparesis
- Memory loss
- Vision Problems
- Weakness of the legs and arms.

Medications which cause or aggravate PML:-

- Rituximab
- Natalizumab
- Alemtuzumab
- Cyclophosmamide
- Prednisolone
- Mycofenolatemofetil
- Tacrolimus
- Dexamethasone

Eligibility Criteria: -

Inclusion Criteria:

- Diagnosis of PML confirmed by detection of JCV DNA in CSF.
- Age within 18 to 70 years.
- Patient who has given his/her informed consent, and signed the consent form.
- Non pregnant and non-lactating women.
- Patients willing to undergo MRI and other study procedures.
- Life Expectancy at least 1 year
- Onset of PML symptoms within 6 months prior to study (Infection in Initial stage)

Exclusion Criteria:

- Other opportunistic infection of the central nervous system such as toxoplasmosis, multiple sclerosis, neurosyphillis etc.
- Patients with severe malignancies such as brain tumour and Kaposi Sarcoma and diseases such as hepatitis and Sickle cell anaemia.
- A history of drug abuse in the 6 months prior to screening.
- Medical contraindication to MRI (i.e., devices such as a cardiac pacemaker or infusion pump, other metallic implants, metallic foreign objects, body piercings that cannot be removed)
- Woman of child bearing potential not protested by effective contraceptive method of birth control and/or are willing or unable to be tested for Pregnancy.
- Active severe mental illness (e.g., depression, anxiety, psychosis, and schizophrenia).
- Hypersensitivity to mirtazapine, serotonin inhibitors or to any component of these drugs.
- Current treatment with Mirtazapine due to other ailments.
- Patients with Current participation in other clinical trials.

Primary outcome measure:-

The primary objective of the study was to explore whether Mirtazapine can delay or stop progression of PML at initial stages as measured by JC virus load in cerebrospinal fluid (CSF).

Secondary outcome measure:-

The secondary objective of the study was to explore whether Mirtazapine can delay or stop progression of PML at initial stages based on neurological deterioration, Magnetic Resonance Imaging (MRI) measures of brain lesion evolution or the formation of new lesions, and mortality.

Primary Endpoints:-

- **Change from Baseline to week 8,16 and 24 in JC Virus Load**(viral load less than 500 copies/ml) [Time frame :- week 0, 8, 16, 24]

Secondary endpoints:-

- Marked improvement in brain lesions from week 0 to week 16 and 24 for the experimental arm v/s placebo arm.
- Change from baseline to week 16 and 24 in the Expanded Disability Status Scale (EDSS) Score and normal range of CD4+ and CD8+.
- Change from baseline to week 16 and 24 in Karnofsky Performance scale.
- Change from Baseline to Week 16 and Week 24 in Participants' pain scores using a Visual Analog Scale (VAS).

Rescue Treatment Strategy:-

Patients diagnosed with PML infection at initial stage are recruited in the study. The stage of PML is detected mainly by viral load in cerebrospinal fluid. Normal range of CSF is less than 500 copies/ml. Patient is given Mirtazapine 15 mg for first three days and then it is given weekly for 6 months. If there is no improvement in viral load or if viral load increases than immediately the patient is given approved therapy like drugs such as IL-7, Imatinib, CMX001 and other treatment regimen to prevent further increase in viral load.

Schedule of Assessment

	Screening	Treatment							Follow up	
Procedures	-14 days	Day 1	Day 28	Day 56	Day 84	Day 112	Day 140	Day 168	Day 196	Day 224
	-14 to 0	Week 0	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 36	Week 48
Day	3days/ week									
Informed Consent	×									
Screening; Inclusion/Exclusion Criteria	×									
Medical History, Demographics	×									
Randomization		×								
Physical Examination	×									
CD4+ and CD8+ counts		×				×		×		
Vital Signs	×	×	×	×	×	×	×	×	×	×
Dose		×	×	×	×	×	×	×		
CSF determination		×				×		×		
Brain lesion (MRI)		×				×		×		
Symptomatic		×	×	×	×	×	×	×	×	×

assessment										
Treatment History (Prior medication)	×									
Concomitant medication		×	×	×	×	×	×	×		
Adverse events		×	×	×	×	×	×	×	×	×
Visual Analog Pain Scale (VAS)		×				×		×		
EDSS Score		×				×		×		
Karnofsky Performance scale		×				×		×		

7.1 Schedule of Assessement of Trial Design

Vital signs, concomitant medications, adverse effects, pain analogue scale, will be performed on before or after dosing.

Randomization is done by sealed envelope method.

Dose of Mirtazapine is 15mg for first three days and then it is given weekly.

CHAPTER-9

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ABSTRACT

Objectives:

Mandibular resection for oral cancer is mainstay and prime requirement to achieve an acceptable boundary of tumor removal. Mandibular resection has been related with a poor health-related quality of life (HRQOL). The aim of this study was to assess health-related quality of life in patients who have undergone mandibular resections of oral cancer and reconstructed with Pectoralis Major Myocutaneous flap.

Study Designs:

There were 192 consecutive patients between 2011 and 2014 who were treated for head and neck cancer, amongst them 65 patients were having oral cancer and treated with mandibular resections. HRQOL was assessed by University of Washington Quality of Life (UW-QOL) questionnaire version four after 3-12 months postoperatively.

Results:

In the UW-QOL the best-scoring domain was shoulder, recreation and pain, whereas the lowest scores were for speech, chewing and swallowing.

Conclusions:

Mandible reconstruction with Pectoralis Major Myocutaneous flap would have significantly influenced on patients' quality of life and oral functions. The socio-cultural data shows a low level of education and low economic status for the majority of patients.

Key words:

Health-related quality of life, Pectoralis Major Myocutaneous flap, UWQOLv4,

CHAPTER-2 INTRODUCTION

Head and Neck Cancer

Cancer of the region from the neck and above is referred to as Head and Neck Cancer (HNC) or Oral Cancer.

Most head and neck cancers begin in the cells that line the mucosal surfaces in the head and neck area, e.g., mouth, nose, and throat. Normal mucosal cells look like scales (squamous) under the microscope, so head and neck cancers are often referred to as squamous cell carcinomas. Some head and neck cancers begin in other types of cells. For example, cancers that begin in glandular cells are called adenocarcinomas.

Cancers of the oral cancer are further identified by the area in which they begin:-

- Oral cavity
- Salivary glands
- Paranasal sinuses and nasal cavity
- Lymph nodes in the upper part of the neck.
- Pharynx
- Nasopharynx
- Oropharynx
- Hypopharynx [1,2]

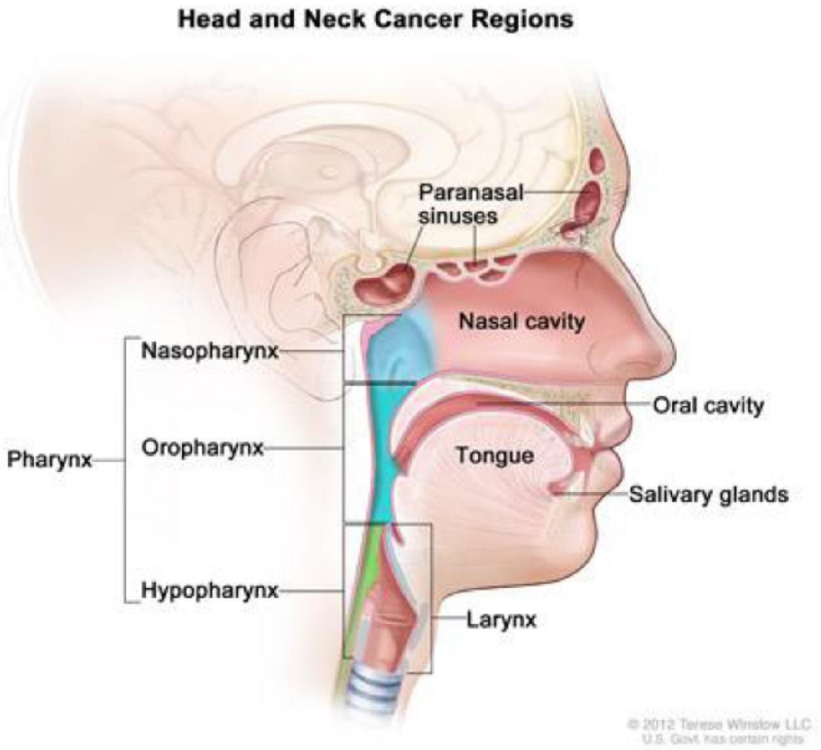

Figure 2.1 Head and Neck Cancer Regions

Epidemiology

Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide. Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, central and Eastern Europe, Spain, Italy, Brazil and among African Americans in the Unites States. Mouth and tongue cancers are more common in the Indian subcontinent, nasopharyngeal cancer is more common in Hong Kong, and pharyngeal and/or laryngeal cancers are more common in other populations. [3]

In the United States, head and neck cancer accounts for 3 percent of malignancies, with an estimated 55,000 Americans developing head and neck cancer annually and 12,000 dying from the disease. The incidence of laryngeal cancer, but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African-American men. The

mortality associate with both laryngeal and oropharyngeal cancer is significantly higher in African American men, which may reflect the lower prevalence of HPV positivity. [3]

Etiology/Pathophysiology

Head and neck cancer occurs because of the molecular changes from dysplasia to carcinoma. The accumulation of these altered cells results in tumour development. The combined effect of molecular changes and microenvironment changes results in tumour invasion and metastasis. Genetic changes leads to protein changes and accumulation of these altered protein changes results in to the formation of malignancy. Altered pathways in head and neck cancer include p53, epidermal growth factor receptor, signal transducer and activator of transcription 3 and vascular endothelial growth factor receptor, among other important molecules that may serve as therapeutic targets.[4]

Risk factors/Causes

- Tobacco (chewing and snuffing)
- Alcohol
- Sun exposure (lip); possibly human papillomavirus (HPV) infection
- Diagnostic x-rays / radiation therapy
- Industrial exposures, such as wood or nickel dust inhalation
- Epstein-Barr virus
- Exposure to airborne particles of asbestos [5]

Signs & Symptoms

- Lump or sore that does not heal
- Sore throat that does not go away
- Difficulty swallowing

- Change or hoarseness in the voice
- Oral cavity: A white or red patch on the gums, tongue, or lining of the mouth; a swelling of the jaw that causes dentures to fit poorly or become uncomfortable; and unusual bleeding or pain in the mouth.
- Nasal cavity and sinuses: Sinuses that are blocked and do not clear, chronic sinus infections that do not respond to treatment with antibiotics, bleeding through the nose, frequent headaches, swelling or other trouble with the eyes, pain in the upper teeth, or problems with dentures.
- Salivary glands. Swelling under the chin or around the jawbone; numbness or paralysis of the muscles in the face; or pain that does not go away in the face, chin, or neck. [5]

Diagnosis/Physical Examination/Tests

- Physical examination may include visual inspection of the oral and nasal cavities, neck, throat, and tongue using a small mirror and/or lights. The doctor may also feel for lumps on the neck, lips, gums, and cheeks.
- Laboratory tests examine samples of blood, urine, or other substances from the body.
- X-rays create images of areas inside the head and neck on film.
- Endoscopy is the use of a thin, lighted tube called an endoscope to examine areas inside the body. The type of endoscope the doctor uses depends on the area being examined. For example, a laryngoscope is inserted through the mouth to view the larynx; an esophagoscope is inserted through the mouth to examine the esophagus; and a nasopharyngoscope is inserted through the nose so the doctor can see the nasal cavity and nasopharynx.
- CT (or CAT) scan is a series of detailed pictures of areas inside the head and neck created by a computer linked to an x-ray machine.
- Magnetic resonance imaging (or MRI) uses a powerful magnet linked to a computer to create detailed pictures of areas inside the head and neck.

- PET scan uses sugar that is modified in a specific way so it is absorbed by cancer calls and appears as dark areas on the scan.

Biopsy is the removal of tissue. A pathologist studies the tissue under a microscope to make a diagnosis. A biopsy is the only sure way to tell whether a person has cancer.

- If the diagnosis is cancer, the doctor will want to learn the stage (or extent) of disease. Staging is a careful attempt to find out whether the cancer has spread and, if so, to which parts of the body. Staging may involve an examination under anesthesia (in the operating room), x-rays and other imaging procedures, and laboratory tests. Knowing the stage of the disease helps the doctor plan treatment.

TNM staging:

- T describes the size of the tumour.
- N describes whether the cancer has spread to the lymph nodes and which nodes are involved. For example, N0 means that no lymph nodes are affected, while N1 means there are cancer cells in the lymph nodes.
- M describes if the cancer has spread to another part of the body. For example, M0 means the cancer has not metastasized to other parts of the body.

Biomarkers:

- EGF, EGFR, IL-8, tPAI-1, AFP, MMP-2, MMP-3, IFN-□, IFN-□, IP-10, RANTES, MIP-1□, IL-7, IL-17, IL-1R□, IL-2R, G-CSF, mesothelin, IGFBP-1, E-selectin, cytokeratin (CK)19, V-CAM, and CA-125

Treatment & Management

Treatment includes the following

– Chemotherapy

– Radiation therapy

– Surgery

– Combination Chemo-Radio therapy

Chemotherapy:

- Alkylating agents: Cisplatin
- Antimetabolites: Methotrexate
- Antitumor Antibiotics: Doxorubicin, Bleomycin
- Alkaloids: Vincristine, Vinblastine
- Taxanes: Paclitaxel

Radiation therapy:

- Radiotherapy can be given in two ways:
  - From outside the body as external beam radiotherapy. A beam of x-rays or electrons is directed at the cancer from a large machine called a linear accelerator. This is the most common way of giving radiotherapy to the head and neck area.
  - By putting a radioactive source into the tumour and leaving it there for a few days. This is known as internal radiotherapy, interstitial radiotherapy or brachytherapy.

Surgery:

- The surgeon may remove the cancer and some of the healthy tissue around it.
- Lymph nodes in the neck may also be removed (lymph node dissection), if the doctor suspects that the cancer has spread.
- Surgery may be followed by radiation treatment.

Chemoradiation therapy:

- Chemoradiation is often the main treatment for advanced head and neck cancers. It may be used as follows:-
- To treat cancers that cannot be removed with an operation.
- To treat cancersin hard to reach areas such as the nasopharynx or throat when surgery could cause unacceptable changes to speech or swallowing.

Patient Management

- Head and neck surgery often changes the patient's ability to chew, swallow, or talk. The patient may look different after surgery, and the face and neck may be swollen.
- After a laryngectomy (surgery to remove the larynx), parts of the neck and throat may feel numb because nerves have been cut.
- If lymph nodes in the neck were removed, the shoulder and neck may be weak and stiff.
- Patients who receive radiation to the head and neck may experience redness, irritation, and sores in the mouth; a dry mouth or thickened saliva; difficulty in swallowing; changes in taste; or nausea.
- Other problems that may occur during treatment are loss of taste, which may decrease appetite and affect nutrition, and earaches (caused by hardening of the ear wax).
- Patients may also notice some swelling or drooping of the skin under the chin and changes in the texture of the skin.
- The jaw may feel stiff and patients may not be able to open their mouth as wide as before treatment.
- Patients may have side effects such as lower resistance to infection, sores in the mouth and on the lips, loss of appetite, nausea, vomiting, diarrhoea, and hair loss.
- They may also feel unusually tired and experience skin rash and itching, joint pain, loss of balance, and swelling of the feet or lower legs.

Recommendations:

- Stop smoking
- Cut down on alcohol
- Maintain good oral hygiene
- Eat healthily
- Regular dental check-ups and treatment

- Patient counseling [5]

Supportive care

The SPIKES protocol (Setting, Perception, Invitation, Knowledge, Empathy and Strategy) can be a helpful framework for head and neck oncology. This includes taking adequate time to talk to the patient, asking their understanding of the disease and inviting them to express how much they want to know, how they want to be told, and who they want to have with them. Language used should be understandable, with silences to allow news to be taken in. Clinicians should show empathy to the range of emotions presented by the patient and the family, and patient should leave the consultation with a plan of care.[6]

Quality of Life (QOL)

The World Health Organization defines QOL as "an individual's perception of their position in life, in the context of the culture and values systems in their life, and in relation to their goals, expectations, standards, and concerns"

QOL measures seek to obtain a comprehensive, multi-dimensional picture of the patient's "total health related experience."

Quality of Life (QOL) has become an increasingly important outcome measure for patient's undergoing treatment for a wide array of illnesses.

Length of survival alone is an unsatisfactory measure of the success of treatment; the quality of survival needs to be evaluated.

QOL is a global construct that reflects a patient's general sense of well-being.

It is by definition multi-dimensional and reflective of the patient's point of view. Health related issues are among the many factors that may influence QOL.

Since Head and Neck Cancer (HNC) affects structures that are critical for normal functions such as speech and swallowing, and treatment may lead to deformities that adversely impact psychosocial functioning, there is particular interest in assessing QOL in this cohort of patients.

Whether routine use of QOL measures in the clinical setting is beneficial to patients or not has yet to be determined.

Further studies are warranted.

Significance of QOL in HNC:

- QOL data can provide information that guides health care related decision making on several levels.
- First it can help shape public policy and health care decisions made by governmental and private institutions.
- It can also guide the research agenda of pharmaceutical companies and cooperative groups.

- Most importantly, QOL measurement can provide information to guide clinical decision making.

- QOL studies should inform the practitioner about the impact of specific treatments on outcomes.
- This information can then be shared with patients and used to help make decisions regarding treatment options.

By providing concrete information about outcomes, QOL studies can

- Facilitate communication between a physician and their patient
- Identify problems that have a significant impact on QOL
- Guide the physician to screen for problems that impact QOL
- Help physicians prioritize the treatment of problems that develop during treatment.

Aim and Objectives

The routine use of quality of life questionnaires among cancer patients enables health practitioners to discover in which areas and to what extent patients find their lives affected by the treatment they receive and its consequences. This allows health practitioners to provide information and treatments which are better adapted to patient needs.

This study aimed to investigate the health-related QOL characteristics in Oral Cancer patients reconstructed with PMMF with the following objectives:

- To evaluate the compatibility of PMMF at both donor and recipient sites.
- To assess the quality of Life of oral cancer patients after reconstruction with PMMF.
- To investigate the risk factors and to find out correlationsbetween all 12 domains, parts affected and risk factors.

CHAPTER-3 REVIEW OF LITERATURE

3. Review of Literature

3.1 Background of Quality of Life

Quality of Life implicates on the patient's state of well-being. Questionnaires raise the important issue of what is "quality of life"? Something known that cannot be told, whilst to the researcher it is a difficult measurement problem, and to the clinician it is just one of many other equally relevant inputs into a clinical judgment.

Health-Related Quality of Life (HRQOL) is an important outcome parameter following treatment for head and neck cancer. The value of this concept has become established during the last decade. The impact of head and neck cancer and its treatment can have such a profound detrimental effect on function and well-being that it is essential that the patient's perspective is taken into account. Two national bodies, the British Association of Head and Neck Oncologists and the British Association of Otorhinolaryngologists-Head Neck Surgeons, both recommend that HRQOL should be longitudinally recorded. Questionnaires give a structured insight into the patient's point of view. They facilitate multidisciplinary team working with the recognition of poor outcome groups, better information for the patient and their caregivers, and the opportunity to identify problem areas and target support/intervention.

The choice of the HRQOL questionnaire depends on the purpose of the study, its design and the available resources. Certain questionnaires may be more applicable in routine practice and others in a research setting.[7]

3.2 Questionnaires

It is time consuming and a logistical challenge to ensure patients self-complete questionnaires before treatment and at regular intervals subsequently. Very few units are currently collecting HRQOL information and one of the problems has been the selection of the most appropriate questionnaire. There will never be a perfect head and neck questionnaire and there is a choice between about 14 validated measures. The most commonly used are the EORTC, FACT and UW-QOL. However HRQOL data collection

remains a low priority in many units. One reason for this is that some questionnaires are too long or complicated for members of the head and neck team, including the patient, and seem more suited to research. One questionnaire that has emerged as a simple yet clinically relevant measure suitable for routine clinical practice is the University of Washington questionnaire (UW-QOL).[8]

3.3 The University of Washington Questionnaire

In the original description, Hassan and Weymuller stated that „the advantages of the UW-QOL head and neck questionnaire are that 1) It is brief and self-administered, 2) It is multi-factorial, allowing sufficient detail to identify subtle change, 3) It provides questions specific to head and neck cancer, and 4) It allows no input from the health provider, thus reflecting the QOL as indicated by the patient.[9]

The current version 4 of the UW-QOL questionnaire consists of 12 single question domains, these having between 3 and 6 response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response.

The domains are **pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood** and **anxiety**. Another question asks patients to choose up to three of these domains that have been the most important to them. There are also three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. In regard to their overall QOL patients are asked to consider not only physical & mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life. The whole questionnaire focuses on current patient health and quality of life within the past 7 days.[10]

3.4 Scoring of UW-QOL domains

The UW-QOL has domains based upon discrete ordinal responses. Scoring is scaled to so that a score of 0 represents the worst possible response, and a score of 100 represents thebest possible response. Scoring is scaled in equal stages from 0 to 100 to reflect the

number of possible responses. Thus the pain domain has 5 possible responses which are scored as 0, 25, 50, 75 & 100.

3.5 Global Questions

The UW-QOL has domains and general questions based upon discrete ordinal responses. The UW-QOL asks three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. These are now also scaled from 0 to 100 to enable ease of presentation of all key results using the same 0 to 100 scale. The general question asking about overall QOL has 6 possible responses which are scored as 0, 20, 40, 60, 80 & 100.[7]

3.6 Important question

This asks about which three domain issues were the most important during the past 7 days. Patients are asked to choose up to 3 domains,[11]

Chang et al conducted a study with the aim of translating the UW-QOL questionnaire version 4 into the Korean language and carrying out an initial validation study. 56 patients completed Korean versions of UW-QOL, the Beck Depression Inventory and the World Health Organization Quality of Life-BREF and various expected correlations were confirmed first between the two UW-QOL subscales (Spearman 0.54 $p < 0.001$) and then of these subscales with the other concurrent measures. Lower (worse) UW-QOL scores were seen for later stage patients in all the domains.[12]

Jornet et al conducted a project to evaluate the quality of life in patients undergoing treatment for head and neck cancer in the Murcia region (Spain). The Quality of Life (QOL) of 109 patients suffering head and neck cancer was assessed using Spanish translations of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Head and Neck Cancer Module(QLQ-H&N35). The questionnaires‟ scales and single items were compared according to age, sex, tumour location, stage of cancer and treatment type. With regard to the stage of cancer, early stages obtained better scores than advanced ones. Patients who

underwent surgical treatment combined with adjuvant radiotherapy and chemotherapy generally showed lower scores.[13]

Laraway et al conducted a review to systematically search published papers that report UW-QOL questionnaire's use and identify common themes. A total of 66 papers were included in the study, out of which 21 were on functional outcome, 25 on predictors of HR-QOL, 19 on development or validation of the questionnaire, and one clinical trial. The questionnaire was first used in the USA and was written in English, but several translations have since been done which show its cross-cultural application. Translations include simplified Chinese, Hindi and Marathi, Brazilian Portuguese, as well as Italian, German, Norwegian, Malay, Greek, Japanese, and Dutch.

3.7 Reconstruction Methods

After removal of tumour cells, the functional and aesthetic outcomes are negatively affected. Surgical removal of the primary lesions and excisions of the lymph nodes forms the mainstay of treatment in majority of the cases. The aim of reconstructive surgery after surgical resection in oral cancer malignancies is to restore structure and function as soon as possible with minimum trauma to the patient.

Thus to overcome the defects and to improve aesthetic appearance, reconstruction methods are used to ensure the good quality of life after the cure of cancer.

Various types of reconstruction methods are used which are listed as follows:-

1. Facsiocutaneous free flaps
    - Radial forearm
    - Lateral arm
    - Lateral thigh
2. Muscle and Musculocutaneous free flaps
    - Rectus abdominis
    - Lattisimus dorsi
3. Composite free flaps
    - Radial forearm
    - Fibula
    - Scapular/Parascapular
    - Ilium

As malignant tumour are more prevalent in India, Incidence being one third of all new cancer patients and also most of these patients present late in the course of the disease, tumour resection becomes mandatory for them to remove further invasion of tumour cells. Pectoralis Major Myocutaneous Flap is widely used as it is quick and easy to

prepare, reliable and sufficiently close to most oral cancer sites. Its rich blood supply makes the flap extremely safe.

Ariyan and krizek were the first to report the use of PMMFin Head and Neck reconstruction.

Since then this flap has earned the synonym “the workhorse for head and neck reconstructive surgery”

Advantages of Pectoralis major Myocutaneous pedicle flap (PMMF) is as follows:-

- This flap offers one-stage reconstruction.
- The patient's position need not be changed intraoperative.
- This flap provides a large cutaneous island that can be used for defects involving 2 epithelial surfaces.
- The muscular part covers neck structures protecting the carotid artery, especially in patients who have undergone radiation therapy.

Now a days Tissue engineering and Microvascular techniques are used as recent advances to overcome bone defects but PMMF are used because of its versatility and cost effectiveness.

The PMMF is a flap for huge defects in head and neck reconstructive surgery, in particular when a bulky flap is needed in order to cover the carotid artery.

Thus it can be concluded that PMMF is the most versatile flap used for head and neck reconstruction.[14-16]

CHAPTER-4 METHODOLOGY

Methodology

4.1 Study design

Prospective,Single-Centric study involving Oral Cancer patients.

4.1.1 Site of Study

Shrey Hospitals Pvt Ltd, Navrangpura, Ahmedabad.

4.2 Study Population

Sample Size: - 65

There were 192 consecutive patients between 2011 and 2014 who were treated for head and neck cancer, amongst them 65 patients were having oral cancer and treated with mandibular resections. HRQOL was assessed by University of Washington Quality of Life (UW-QOL) questionnaire version four after 3-12 months postoperatively.

4.2.1 Inclusion Criteria

- Adults from age 19 years to 80 years.
- Patients diagnosed and treated from Oral Cancer.
- Patients of whom surgery has been completed.
- Patients on Chemotherapy and follow-up.

4.2.2 Exclusion Criteria:

- Age below 19 years and above 80 years.
- Adults having any other cancer except that of Oral Cancer.
- Severe co morbid diseases and No healthy volunteers.

4.3 Study Methodology:

A prospective, single centric study was designed in which the patients of Oral Cancer after treatment and who were disease free after 6 months of the treatment were recruited and UW-QOL was filled which includes parameters such as Pain, Appearance, Activity, Recreation, Swallowing, Chewing, Speech, Shoulder, Taste, Saliva, Mood and Anxiety were assessed during the past seven days of operation. On the basis of these parameters quality of Life of oral cancer patients was evaluated. Also patient's compatibility with reconstruction with Pectoralis Major Myocutaneous Flap was assessed.

4.4 Ethical Consideration

Study protocol was reviewed and approved by the Institute of Pharmacy, Nirma University. IEC/NU/15/2/10th April 2015.

4.5 Study Evaluation Criteria

- Pain
- Appearance
- Activity
- Recreation
- Swallowing
- Speech
- Shoulder
- Taste
- Saliva
- Mood
- Habits
- Education
- Socioeconomic status
- Occupation
- Anxiety
- Age
- Gender
- Habits: chewing tobacco or smoking, alcohol
- Education
- Occupation
- Comorbidities
- Compatibility with pectoralis major Myocutaneous flap

4.6 Statistical Analysis

Data were recorded, and then analysed with the help of the Statistical Package for the Social Sciences (SPSS version 19). Univariate analysis of variance was carried out and P-value less than 0.005 were accepted as significant. Quantitative results were expressed as mean±SD.

CHAPTER-5 RESULTS

RESULTS

Sixty-five patients with oral cancer were included in this analysis. All patients completed the questionnaire during their visit to the hospital for follow-up. Of the 65 patients who completed questionnaires, there were 55 men and 10 women with a median age of 50.5 (range 30–60)

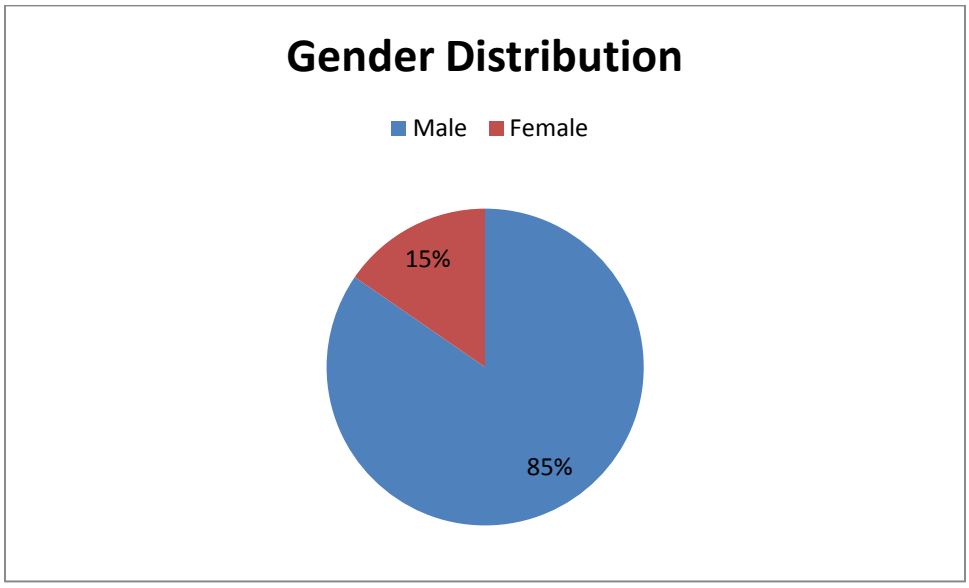

Figure 5.1: Gender Distribution of oral Cancer Patients

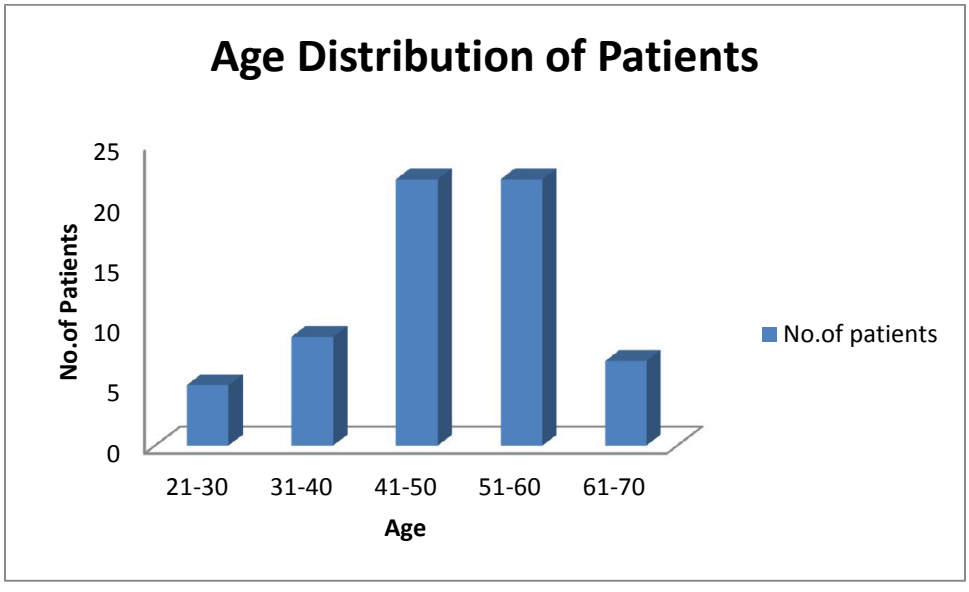

Figure 5.2: Age distribution of oral Cancer Patients

Table:5.1 depicts that Buccal mucosa (N=42, 64.61%) and tongue (N=12, 18.46%) were the most common sites (Followed by alveolus (N=7, 10.76%) and Retro molar trigon (N=4, 6.15%) Forty-nine patients of 65(75.38%) were classified as T1–T2, while 16 (24.61%) were classified as T3–T4. The postoperative follow-up period ranged from 3 months to 2 years, and the mean follow-up point was 2.5 years. 46 patients were between 1 and 3 years after treatment and the remaining 19 patients had been treated before 3 months. It was observed that buccal mucosa cancer is more prevalent among other cancers in Indian ethnicity.

Table:-5.1 patient's proforma

Variables	**N**	**%**
Age		
<50 years	36	55.38
≥50 years	29	44.61
Gender		
Male	55	84.61
Female	10	15.38
Primary Tumor sites		
Buccal Mucosa	42	64.61
Tongue	7	10.76
Alveolus	12	18.46
Retro molar Trigon	4	6.15
Treatment method		
Post-Operative Radiation	46	70.76
Post-operative Radiation and Chemotherapy	19	29.23

Tumor Classification		
T1N0	13	20
T1N1	1	1.53
T2N0	25	38.46
T2N1	3	4.61
T2N2	7	10.76
T3N0	2	3.07
T3N2	1	1.53
T4N0	8	12.30
T4N1	1	1.53
T4N2	4	6.15

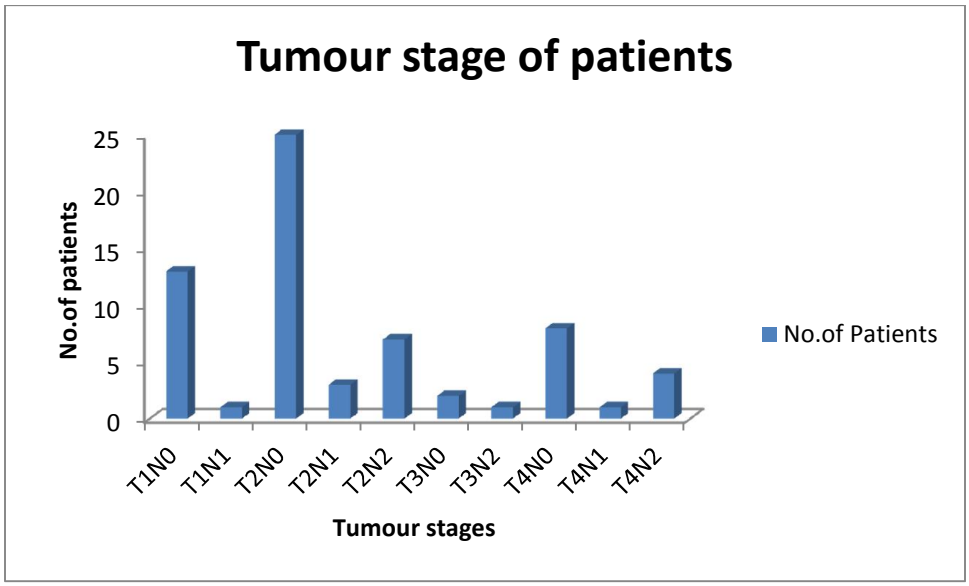

Figure 5.3 Classification of Tumor Stages of oral Cancer Patients

Quality of life UW-QOL: The scores for 12 disease-specific domains and the importance of each domain are shown in table 5.2The best-scoring domain was shoulder and recreation, with the main score of 79.53 and 73.84 respectively. The worst score of the domains are chewing, swallowing and speech, with the main score of 46.15, 48.69, and 53.23 respectively.

Amongst selection of the three domains over the past 7 days chewing was considered as most important aspect followed by speech and swallowing. Domains such as recreation, shoulder and mood were considered least important to the patients.

Table:-5.2 Domains of UWQOL (v4) questionnaire

UWQOL(v4) Domains	Mean	SD	Median	Rank order
Pain	68.84	28.30	75	10
Appearance	63	19.78	75	7
Activity	55.38	21.87	50	4
Recreation	73.84	22.72	75	11
Swallowing	48.69	22.50	30	2
Chewing	46.15	22.19	50	1
Speech	53.23	27.50	70	3
Shoulder	79.53	22.46	70	12
Taste	56.61	29.22	70	5
Saliva	58.30	34.39	70	6
Mood	64.30	29.08	75	8
Anxiety	64.53	25.07	70	9

Chewing, speech and swallowing parameters were significant having p-value less than 0.005.

These analysis was carried out using univariate analysis of variance.

About sixty percent patients had low education level. Twenty-two (33.84%) patients did not complete education above 12^{th} standard. Forty-three patients (66.15%) were having education below 12^{th} standard. Consumption of pan, guthka, beedi, tobacco and smoking

were highly seen among male patients. Quality of life was negatively affected in higher tumor stages.Some patients were unable to read and write and they need help to complete the questionnaire.

Table:-5.3 Demographic Details

Variables	N	%
Employment status		
Employed	34	52.30
Homemaker	10	15.38
Medical leave	5	7.69
Retired	11	16.92
Unemployed	5	7.69
Educational status		
Above 12th	22	33.84
Below 12th	43	66.16
Addiction		
Smoking	2	3.07
Tobacco	49	75.38
No addiction	14	21.53
Marital status		
Married	56	86.15
Unmarried	2	3.07
Widow/widower	7	10.76

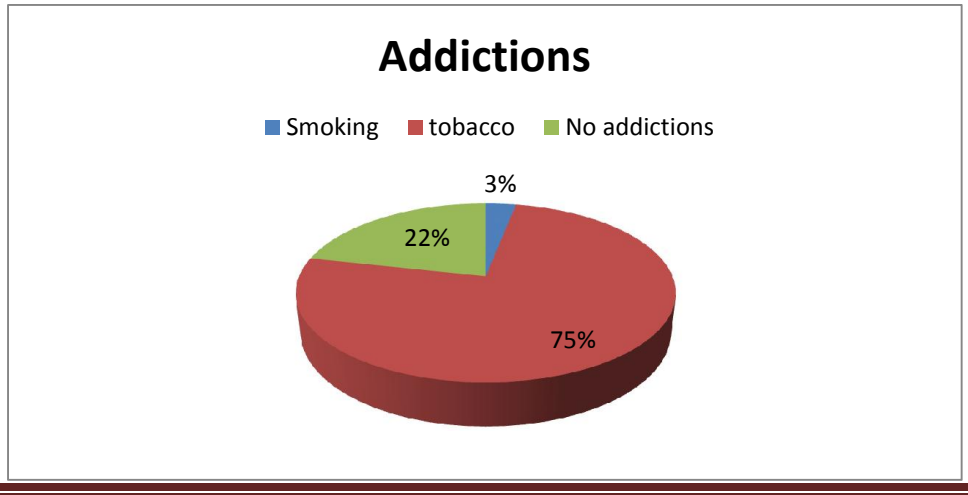

Fig:-5.4 (%)calculation of Addiction to the patients.

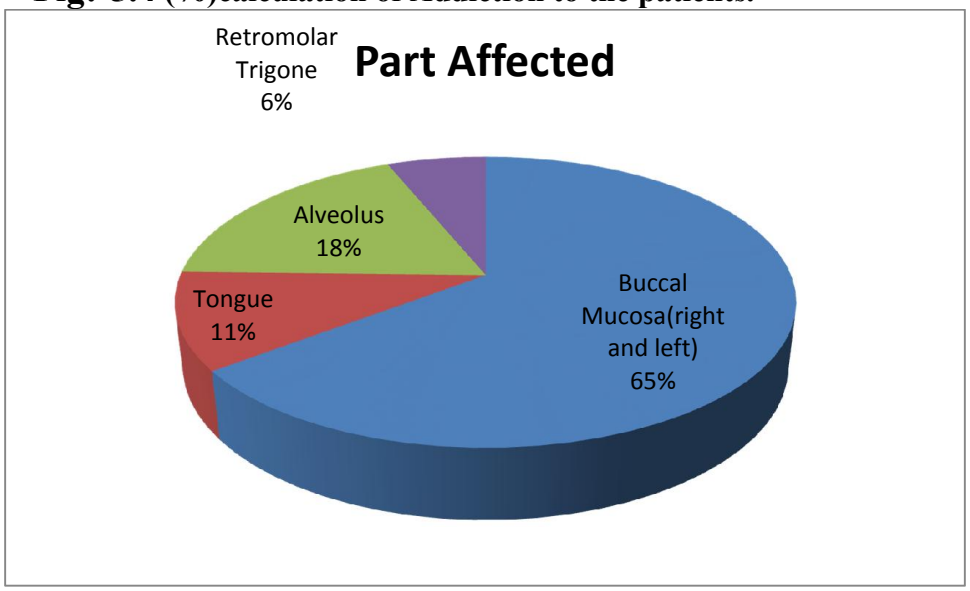

Figure 5.5: Parts affected of Oral cavity

Positive co-relation with age and risk factor was found and majority of the patients were found to have addiction of Tobacco consumption and smoking.

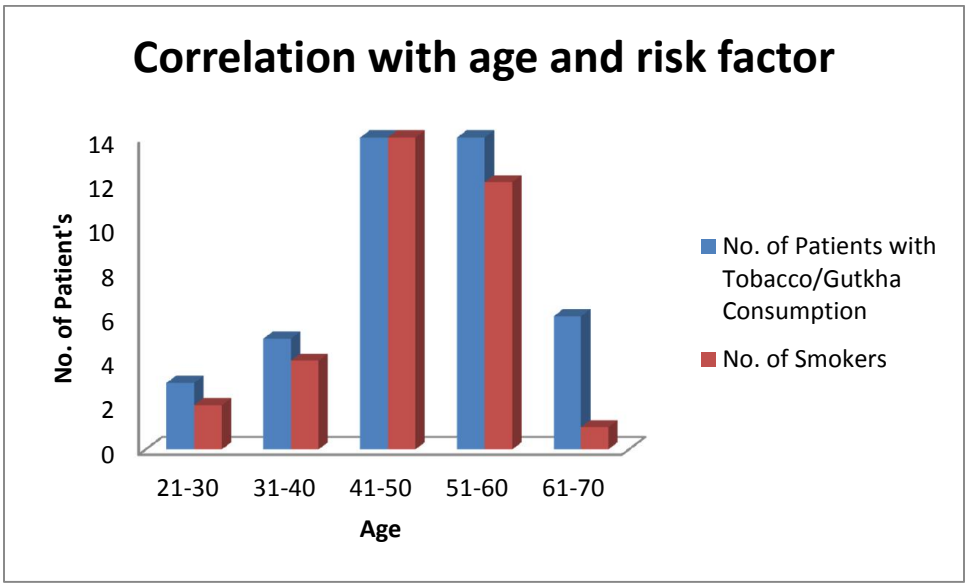

Figure: - 5.6 Correlation with age and risk factor

It was found that the age group of 41-61 has the highest rates of Tobacco/Guthka consumption and alcohol addiction.

Table:-5.4 Quality of Life Score Distribution

Avg. QOL Score Range	No. of Patients
0-10	
11-20	
21-30	
31-40	3
41-50	10
51-60	13
61-70	17
71-80	3
81-90	
91-100	2

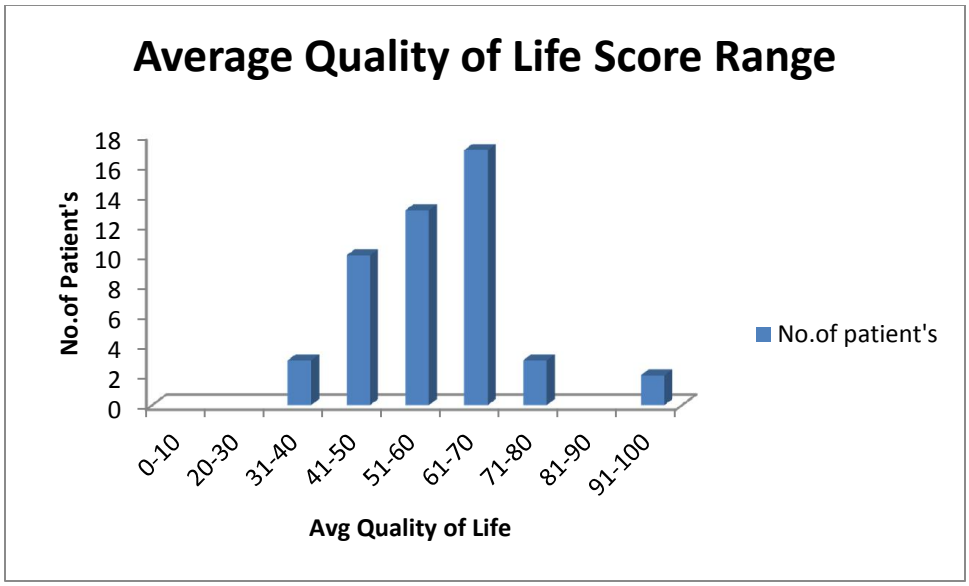

Figure 5.7: Average QOL Score range

A majority of the patients (30) have their Avg. QOL Scores in the near median range of 51-70, and a large number of these patients have scores below the same range which represents their reduced QOL. Only 6 patients had their QOL Scores above 70.

Table:-5.5 Functionality Score Distribution:

Avg. Functionality Score Range	No. of Patients
0-10	0
11-20	2
21-30	2
31-40	6
41-50	9
51-60	10
61-70	20
71-80	13
81-90	4
91-100	3

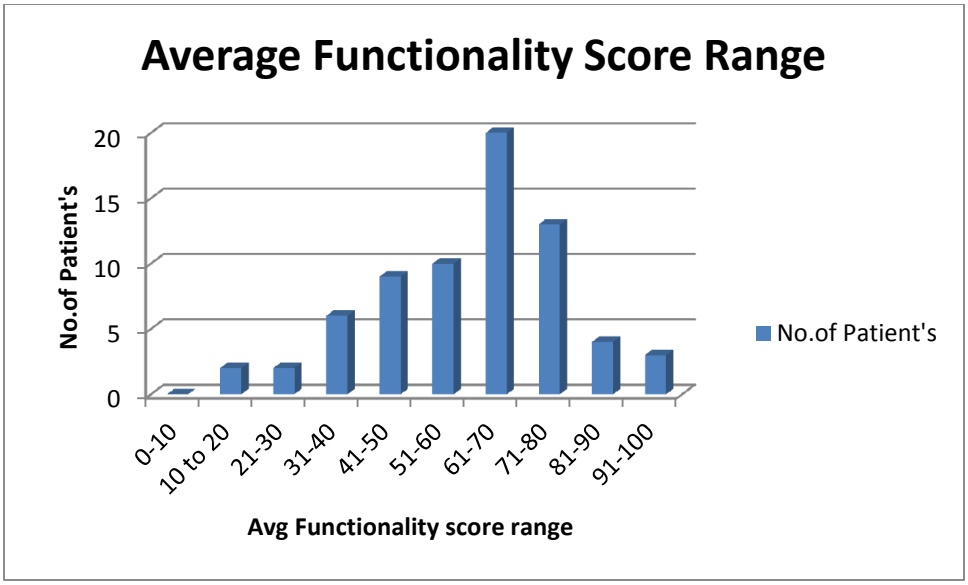

Figure: 5.8 Functionality Score based Distribution of Patients

A majority of the patients (N=20) have median functionality scores (61-70) followed by 10 patients in the range of 51-60. Nineteen patients have scores below 50 and 20 patients have scores above 70.

Table:-5.6 Distribution according to Part Affected

Part Affected	Avg. QOL Score Compared to a Month before Diagnosis	Avg. Functionality Score	Avg. QOL Score
Buccal Mucosa	87.5	64.46	59.16
Tongue	90.33	58.40	56.87
Alveolus	70.53	54.66	51.42
Retro molar Trigon	90.87	63.42	57.42

This table shows the mean scores of patients according to the part affected. It can be seen that the quality of life score compared to one month before diagnosis is good in comparison of Avg. functionality score and average QOL scores.

Table:-5.7 Addiction and Quality of Life Score

Risk Habits / Addiction	Avg. QOL Score Compared to a Month before Diagnosis	Avg. Functionality Score	Avg. QOL Score
Tobacco/*Guthka* (N=49)	78.57	61.08	41.63
Smoking (N=2)	100	80.62	60
None (N=14)	80	64	60

This table shows the mean scores of patients with risk habits/addictions and compares them with those of patients with no such habits/addictions. Quality of Life of Tobacco consumers is very low compared to no addiction group.

CHAPTER-6 DISCUSSION

DISCUSSION

Health related quality of life is an integrated process for the overall treatment of oral cancer patients. The impact of cancer and its later consequences affects quality of patient's life and their families as well. Mandibular resections have their own drawbacks such as it causes unevenness, facial misshape and loss of teeth due to which chewing is compromised. Mandible is involved in crucial activities such as protection of airway passage, support to the tongue and lower dentition. Also it is involved in functions such as speech, mastication and deglutition. Reconstruction of mandibular defects after tumor resection is one of the most challenging problems faced by the plastic surgeons. Also donor-recipient compatibility is very important for the entire reconstruction method. [17]

The Myocutaneous flap as a source of vascularized bone in reconstructive surgery is in wide use

As it ensures more durable blood supply, also defect at the donor site can be primarily closed and provides tissue bulk to cover large defects.

HRQOL has nowadays become a constant provoking question in the assessment of any therapy in oncology. It is time consuming and a logistical challenge to ensure patients self-complete questionnaires before treatment and at regular intervals subsequently, thus a reliable method should be adopted for obtaining complete details of the patient's treatment with ease. In the present study, we have used University of Washington Head and Neck Quality of Life questionnaire (UW-QOL) version four. In the original description, Hassan and Weymuller et al stated the advantages of the UW-QOL head and neck questionnaire are that 1) It is brief and self-administered, 2) It is multi-factorial, allowing sufficient detail to identify subtle change, 3) It provides questions specific to head and neck cancer, and 4) It allows no input from the health provider, Also UWQOL is widely used questionnaire because it is short and easy for patients to complete themselves, thus making it perfect in a hectic outpatient setup. The current version 4 of the UW-QOL questionnaire consists of 12 single question domains, these having different response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response[17].we carried out this study to determine the postoperative HRQOL of these patients and the possible relationship of reconstruction surgery.

The oral specific questionnaire was able to better demonstrate the changes in quality of life due to surgery. We can see that the highest score of UW-QOL subscale in present study was in recreation and shoulder domain. The average score was 73.84±22.72 and 79.53±22.46 respectively, patients scored high in pain (68.84±28.30) and appearance (63±19.78) domains, this indicates that mandible reconstruction with Myocutaneous flap have little effect on pain domain. A noteworthy outcome was the relatively low scores of UW-QOL subscales in this study were in speech and swallowing domains. The average scores were 53.23±27.50 and 48.69±22.50, which indicated that mandible reconstruction with Myocutaneous flap have bad effect on speech and swallowing domains. At the same time we found that patients satisfied with the appearance domains. This may be due to the Pectoralis Major Myocutaneous flap (PMMF) as it provides comparatively satisfactory aesthetic as well as functional reconstruction of mandible defects and thereby obtaining a better aesthetic contour. Though, a significant result was that the lowest score of UWQOL was in chewing (46.15±22.19) domain. This is may be due to mandible defects caused some teeth lost, thus resulting in disorientation of chewing function.

Patients believe that surgery has altered their oral functions to a larger extend. In present study, questionnaires do not contain a section on the effect of the Myocutaneous flap donor site on HRQOL and function. But majority of patients reported no serious or any complications in wound healing. A bit strain in shoulder was observed till the wound healing fully completed, after that no complaints were reported for donor site complications. Also as the donor site is covered under clothes it is well acceptable by the patients. The immediate postoperative donor site morbidity is generally considered to be low and is reported to be in a range between 15% and 55. In our study, 21.42 % of the patients specifically males reported problem of hairs at the defect site ashirsute chest skin is placed intraorally. Some studies have mentioned that apart from only surgery the adjuvant radiotherapy and chemotherapy resulted in reduced weight, altered salivary and physical functions. Also functions such as swallowing and chewing were not as same as before and problems of coughing, and dry mouth increased.46/65 patients in our study (70.76%) were given radiotherapy and 19 patients (29.23%) were given both Radiation and Chemotherapy. Among them 38 patients (58.46%) complained about loss of appetite, dry mouth and weight loss after chemotherapy/radiotherapy or both.There were several

limitations of this study. First, the sample size was limited and may not have had sufficient power to find more valid and proofed data. Secondly, we collected data after patient's treatment during their follow-up, entire pre and post-operative period was not precisely evaluated and so could not fully assess its impact on patient HRQOL over the entire treatment period.[18]

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CHAPTER-9 ANNEXURE

દર્દી માહિતી પત્રક અનં સંમતિ પત્રક

શીર્ષક: યુનિવર્સીટી ઓફ વોશિંગ્ટન પ્રશ્નાવાલી દ્વારા ઓરલ કેન્સર ના દર્દી નુ ઓપેરશન અને સારવાર પછી જીવન ગુણવત્તા નુ માપદંડ-પ્લાસ્ટીક સર્જરી પધ્ધતિ પ્લેક્તોરલીસ મેજર મ્યોક્યુતનિઔસ ફ્લાપ.

નામ: :

ઊમર: :

૧) હું સ્વીકૃત કરું છું કે મેં ઉપર જણાવેલા અધ્યયન ની માહિતી પત્રિકા વાંચી અને સમજી છે તથા મને પ્રશ્ન [ ] પૂછવાની તક મળી છે.

૨) હું સમજુ છું કે અધ્યયન માં મારો સહભાગ સ્વૈચ્છિક છે અને હું ગમે તે રીતે કોઈ પણ કારણ આપ્યા વિના, [ ] મારી તબીબી સારવાર અથવા કાયદેસર અધિકાર ને અસર થયા વિના છૂટી થવા મુક્ત છું.

૩) હું સમજુ છું કે ચિકિત્સીય અધ્યયન ના પ્રયોજક વતી કાર્ય કરતા અન્યો, નૈતિકતા આપ્યા સમિતિ અને [ ] નિયામક સત્તાધિકારી ને વર્તમાન અધ્યયન તેમજ તેને સંભંધિત કરાતા કોઈ પણ વધારાના સંશોધન માટે

મારા સવાસ્થ્ય રેકોર્ડ્સ જોવા મારી પરવાનગી ની જરૂર નહી પડે, પછી ભલે હું અધ્યયન માંથી છૂટી પણ થાઉં. આ માટે પરવાનગી આપુ છું જો કે હું સમજુ છું કે ત્રીજી પાર્ટીને રજુ કરતી અથવા પ્રકાશિત કરતી કોઇપણ માહિતીમાં મારી ઓળખ જાહેર નહિ કરાય.

૪) આ અભ્યાસ શૈક્ષણિક પ્રોજેક્ટ નો એક ભાગ છે અને સ્થાપિત ચિકિત્સા પર આધારિત છે અને કોઈપણ [ ] નવી સારવાર/ મૂલ્યાંકન તેમાં સામેલ નથી તેથી નાણાકીય લાભ / જવાબદારી કોઈ સંશોધકો ઉપર નથી.

૫) હું આ અધ્યન માંથીન ઉદભવતા કોઇપણ વિગત (ડેટા) પરિણામો ના ઉપયોગને જો તે માત્ર વૈજ્ઞાનિક હેતુઓ સર કરાતો હોઈ તો સીમિત ન રાખવા સહમત થાઉં છું. [ ]

૬) હું ઉપર જણાવેલા અધ્યયનમાં સહભાગી થાઉં છું. [ ]

_____ _____

દર્દી/પ્રતિનિધિ ની સહી/અંગુઠા ની છાપ તારીખ

_____ _____

સંશોધક નું નામ અને સહી તારીખ

દર્દીમાહિતીપત્રક

અધ્યયન નું શીર્ષક:યુનિવર્સીટી ઓફ વોશિંગ્ટન પ્રશ્નાવાલી દ્વારા ઓરલ કેન્સર ના દર્દી નુ ઓપેરશન અને સારવાર પછી જીવન ગુણવત્તા નુ માપદંડ- પ્લેક્તોરલીસ મેજર મ્યોક્યુતનિઔસ ફ્લાપ.

સંશોધક નું નામ: દ્રષ્ટી એસ વોરા
હોસ્પિટલ માર્ગદર્શક નું નામ: ડો. ભાર્ગવ મહારાજા
ઇન્સ્ટીટયુટમાર્ગદર્શક નું નામ: ડો. જીજ્ઞા. શાહ

અધ્યયન નો હેતુ:

હેડ એન નેક કેન્સર ભારત માં દરેક કેન્સર મા ખુબજ અગ્રેસર છે. આ કેન્સર પુરુષો મા વધારે થતો જણાય છે. આ પ્રોજેક્ટ નો હેતુ ઓપેરશન પછી દરદી ની જીવન ગુણવત્તા ચકાસવા માટે કરવામાં આવ્યો છે.પ્લાસ્ટીક સર્જરી પધ્ધતિ રડીએલ ફોરારમ ફ્લાપ કર્યા પછી દરદી ની જીવન ગુણવત્તા નું માપદંડ કેવું છે એ ચકાસવામાં આવશે.

અધ્યાય ની પદ્ધતિ:

આ એક સંભવિત અધ્યાય છે. આ અભ્યાસ માં તેમના અલગ અલગ પરિબળો જેમકે દુખાવો,દેખાવ, પ્રવૃત્તિ, મનોરંજન, ગળવું, ચાવવું,વાચા, ખભો, સ્વાદ, લાળરસ,મનોસ્થીતી, ચિંતા, શિક્ષા, રોજગાર,

સ્ટેજ વગેરે પરિબળોની બધી તપાસો ની કેસ રેકોર્ડ ફોર્મ માં નોંધણી કરવામાં આવશે. અને આ વિગતો પરથી ઓરલ કેન્સર ના દરદી ની જીવન ગુણવત્તા ચકાસવા મા આવશે.

અભ્યાસ માં સહભાગી થતા વ્યક્તિઓ નો સમયગાળો: ૬ મહિના.

અભ્યાસ થી સહભાગીઓ ને થતા જોખમો: કંઈ નહિ.

વિગતો ની ગોપનીયતા રાખવાની જવાબદારી: હા

અધ્યયન થી થતા લાભો ગુમાવ્યા વગર તેમાંથી ગમે તે સમયે છુટ્ટા થવાની સ્વતંત્રતા: હા

જે માહિતી આ અધ્યયન માંથી મળી છે તેનો વર્તમાન તથા ભવિષ્ય ના સંશોધનો માટે તથા અન્ય વ્યક્તિઓ માટે ઉપયોગ કરી શકાશે તેનો ઉલ્લેખ કરવો: હા

સંશોધક નું નામ તથા સરનામું:
દ્રષ્ટી એસ વોરા
એ-૪૦૪, નીલકંઠ રેસીડેન્સી
નારણપુરા રેલ્વે ક્રોસિંગ
અમદાવાદ-૩૮૦૦૧૩
મોબાઈલ નં.: ૯૫૮૬૪૮૬૨૩૩

હોસ્પીટલ માર્ગદર્શક નું નામ તથા સરનામું:
ડો. ભાર્ગવ મહારાજા
શ્રેય હોસ્પીટલ
નવરંગપુરા અમદાવાદ

માર્ગદર્શક નું નામ તથા સરનામું:

ડો. જીજ્ઞા. શાહ
HOD, ફાર્મેકોલોજી ડીપાર્ટમેન્ટ,
ઇન્સ્ટીટ્યુટ ઓફ ફાર્મસી, નિરમા યુનિવર્સીટી

INFORMATION FOR PARTICIPANTS

Title of the project:

Health related Quality of Life assessment of oral cancer patients after mandibular resections using UWQOL Questionnaire: Reconstruction with Pectoralis Major Myocutaneous flap.

Name of the investigator/guide:

Principal Investigator: Dr. Bhargav B Maharaja

Co-investigator: Prof. Jigna Shah

Miss Drasty Vora

-Purpose of this project/study:

Head and neck cancers are the most prevalent cancers in India among males. Head and neck cancers are at 6th position for the reason of death and at 1st position for death in males among all cancers. Also in majority of cases patients seem to suffer more from the treatment side-effects instead of their cancer. As a result, it would be necessary to take into consideration patients' mental and physical status during their treatment as a means of consolation and

optimization. The purpose of this study is to assess the Quality of Life scores of patients suffering from oral cancer and compatibility after reconstruction with pectoralis major myocutaneous flap.

Procedure/methods of the study:

- Prospective single centric study.
- Patients of oral cancer whose treatment has been completes and is disease free after six months of the treatment will be recruited and UW-QOL questionnaire will be filled which will include parameters such as Pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety will be assessed. On the basis of these parameters quality of life of oral cancer treated patients will be evaluated.

Expected duration of the subject participation: 6 months

The benefits to be expected from the research to the participants:

Guidance on how to improve quality of life by life style modification in HNC patients is provided and data of patient's quality of life is assessed.

Possible risks expected from the study to the participant: No risk

Maintenance of confidentiality of records: Yes

Investigator:

Drasty Vora

A-404 Neelkanth Residency, Near Naranpura Railway Crossing, Naranpura Ahmedabad-13

Academic Guide:

Prof. Dr. Jigna Shah

HOD, Department of Pharmacology,

Institute of Pharmacy, Nirma University

Hospital Guide:

Dr. Bhargav Maharaja (Ms. Onco)

Cancer Surgeon

Shrey Hospital, Ahmedabad.

Name: _____
Date: _____

University of Washington Quality of Life Questionnaire (UW-QOL)

This questionnaire asks about your health and quality of life **over the past seven days**. Please answer all of the questions by checking one box for each question.

1. **Pain**. (Check one box: ☑)

- ☐ I have no pain.
- ☐ There is mild pain not needing medication.
- ☐ I have moderate pain - requires regular medication (codeine or nonnarcotic).
- ☐ I have severe pain controlled only by narcotics.
- ☐ I have severe pain, not controlled by medication.

2. **Appearance**. (Check one box: ☑)

- ☐ There is no change in my appearance.
- ☐ The change in my appearance is minor.
- ☐ My appearance bothers me but I remain active.
- ☐ I feel significantly disfigured and limit my activities due to my appearance.
- ☐ I cannot be with people due to my appearance.

3. **Activity**. (Check one box: ☑)

- ☐ I am as active as I have ever been.
- ☐ There are times when I can't keep up my old pace, but not often.
- ☐ I am often tired and have slowed down my activities although I still get out.
- ☐ I don't go out because I don't have the strength.
- ☐ I am usually in bed or chair and don't leave home.

4. **Recreation**. (Check one box: ☑)

- ☐ There are no limitations to recreation at home or away from home.
- ☐ There are a few things I can't do but I still get out and enjoy life.
- ☐ There are many times when I wish I could get out more, but I'm not up to it.
- ☐ There are severe limitations to what I can do, mostly I stay at home and watch TV.
- ☐ I can't do anything enjoyable.

5. **Swallowing**. (Check one box: ☑)

- ☐ I can swallow as well as ever.
- ☐ I cannot swallow certain solid foods.
- ☐ I can only swallow liquid food.
- ☐ I cannot swallow because it "goes down the wrong way" and chokes me.

6. **Chewing**. (Check one box: ☑)

- ☐ I can chew as well as ever.
- ☐ I can eat soft solids but cannot chew some foods.
- ☐ I cannot even chew soft solids.

7. **Speech**. (Check one box: ☑)

- ☐ My speech is the same as always.
- ☐ I have difficulty saying some words but I can be understood over the phone.
- ☐ Only my family and friends can understand me.
- ☐ I cannot be understood.

8. **Shoulder**. (Check one box: ☑)

- ☐ I have no problem with my shoulder.
- ☐ My shoulder is stiff but it has not affected my activity or strength.
- ☐ Pain or weakness in my shoulder has caused me to change my work.
- ☐ I cannot work due to problems with my shoulder.

9. **Taste**. (Check one box: ☑)

- ☐ I can taste food normally.
- ☐ I can taste most foods normally.
- ☐ I can taste some foods.
- ☐ I cannot taste any foods.

10. **Saliva**. (Check one box: ☑)

- ☐ My saliva is of normal consistency.
- ☐ I have less saliva than normal, but it is enough.
- ☐ I have too little saliva.
- ☐ I have no saliva.

11. **Mood**. (Check one box: ☑)

- ☐ My mood is excellent and unaffected by my cancer.
- ☐ My mood is generally good and only occasionally affected by my cancer.
- ☐ I am neither in a good mood nor depressed about my cancer.
- ☐ I am somewhat depressed about my cancer.
- ☐ I am extremely depressed about my cancer.

12. **Anxiety**. (Check one box: ☑)

- ☐ I am not anxious about my cancer.
- ☐ I am a little anxious about my cancer.
- ☐ I am anxious about my cancer.
- ☐ I am very anxious about my cancer.

Which issues have been the most important to you <u>during the past 7 days?</u>
Check ☑ up to 3 boxes.

☐ Pain	☐ Swallowing	☐ Taste
☐ Appearance	☐ Chewing	☐ Saliva
☐ Activity	☐ Speech	☐ Mood
☐ Recreation	☐ Shoulder	☐ Anxiety

GENERAL QUESTIONS

Compared to the month before you developed cancer, how would you rate your health-related quality of life? (check one box: ☑)

- ☐ Much better
- ☐ Somewhat better
- ☐ About the same
- ☐ Somewhat worse
- ☐ Much worse

In general, would you say your **health-related quality of life** during the past 7 days has been: (check one box: ☑)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Overall quality of life includes not only physical and mental health, but also many other factors, such as family, friends, spirituality, or personal leisure activities that are important to your enjoyment of life. Considering everything in your life that contributes to your personal well-being, rate your **overall quality of life** during the past 7 days. (check one box: ☑)

- ☐ Outstanding
- ☐ Very good
- ☐ Good
- ☐ Fair
- ☐ Poor
- ☐ Very poor

Please describe any other issues (medical or nonmedical) that are important to your quality of life and have not been adequately addressed by our questions (you may attach additional sheets if needed).

નામ: _____

તારીખ: _____

વોશિંગટન યુનિવર્સિટીની જીવનની ગુણવત્તા વિષેની પ્રશ્નોત્તરી

(UW-QOL v4)

છેલ્લા સાત દિવસો દરમ્યાનની તમારા સ્વાસ્થય અને જીવનની ગુણવત્તા વિશે પુછાતી આ પ્રશ્નોત્તરી છે દરેક પ્રશ્ન માટે કોઈ પણ એક ખાનામાં ખરા ની નિશાની કરીને તમામ પ્રશ્નોત્તરીના પ્રત્યુત્તર આપવા વિનંતી .

૧. **દુખાવો.** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મને કોઈ દુખાવો નથી.
- ☐ મને નજીવો દુખાવો છે પણ કોઈપણ પ્રકારની દવાની જરૂર નથી.
- ☐ મને સાધારણ દુખાવો છે જેના માટે મારે નિયમિત દવા લેવી પડે છે.
- ☐ મને સખત દુખાવો છે કે જે ડૉક્ટરે આપેલ દવાથી રાહત રહે છે. (ઉદાહરણ: મૉરફીન)
- ☐ મને સખત દુખાવો રહે છે અને મને દવાઓથી રાહત રહેતી નથી.

૨. **દેખાવ.** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મારા દેખાવમાં કોઈ જ બદલાવ નથી.
- ☐ મારા દેખાવમાં ગૌણ બદલાવ છે.
- ☐ મારો દેખાવ મને ચિંતિત કરે છે પણ તેમ છતાં હું કાર્યશીલ રહુ છું.
- ☐ મને લાગે છે કે હુ અત્યંત બેડોળ દેખાઉ છુ જેથી મારા દેખાવ ને કારણે હું મારી પ્રવૃત્તિઓ સિમીત રાખું છું.
- ☐ મારા દેખાવને કારણે હું લોકો સાથે ભળતો નથી.

૩. **પ્રવૃત્તિ** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ હું હમેંશાની માફક પ્રવૃત્તિમય રહું છુ.
- ☐ ક્યારેક એવુ બને છે કે, હું પહેલા જેવા વેગથી કાર્ય કરી શકતો નથી પણ તેવું વારંવાર બનતું નથી.
- ☐ હું ઘણીવાર થાકી જતો હોઉ છું તેથી મારી પ્રવૃત્તિઓ ઓછી કરી દીધી છે છતાં હું એમાંથી બહાર આવી જાઉ છું.
- ☐ હું બહાર જઈ શકતો નથી કારણકે મારામાં શક્તિ નથી.
- ☐ હું મોટાભાગે પથારી અથવા ખુરશી માં જ હોઉ છું અને ઘરની બહાર નીકળતો નથી.

૪. **મનોરંજન** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ ઘરમાં અથવા ઘરની બહાર મનોરંજન મેળવવા માટેની કોઇ મર્યાદા નથી.
- ☐ અમુક વસ્તુઓ છે કે જે હું કરી શકતો નથી છતા તેમાથી બહાર નીકળી ને હું જીવનને માંણુ છું.
- ☐ કેટલીક વખત હું ઈચ્છું છું કે હું વધુ વખત બહાર નીકળું, પરંતુ હું તેવું કરી શકતો નથી.
- ☐ હું ખૂબજ મર્યાદીત વસ્તુઓ કરી શકુ છું જેથી મોટાભાગે હું ઘરમાં રહીને ટીવી જોઉ છું.
- ☐ હું મજા માણી શકાય તેવુ કંઈ પણ કરી શકતો નથી.

૫. **ગળવું** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ હું કોઈપણ વસ્તુ હમેંશાની માફક ગળી શકુ છું.
- ☐ હું અમુક સખત ખોરાક ગળે ઉતારી શકતો નથી.
- ☐ હું પ્રવાહી ખોરાક જ ગળે ઉતારી શકુ છું.
- ☐ હું કશુપણ ગળે ઉતારી શકતો નથી કારણકે તે ખોટી જગ્યાએ જઈને ગુંગણામણ પેદા કરે છે.

૬. **ચાવવું** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ હું હમેંશાની માફક ચાવી શકુ છું.
- ☐ હું નરમ-પદાર્થ ખાઈ શકુ છું પરંતુ અમુક ખોરાક ચાવી શકતો નથી.
- ☐ હું નરમ-પદાર્થ ને પણ ચાવી શકતો નથી.

૭. **વાચા** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મારી વાચા હમેંશાની માફક જ છે.
- ☐ મને કેટલાક શબ્દો બોલવામાં તકલીફ પડે છે પરંતુ મારી વાચા ફોન પર સમજી શકાય છે.
- ☐ મારા કુટુંબના સભ્યો અને મારા મિત્રો જ મને સમજી શકે છે.
- ☐ મને સમજી શકાય તેમ નથી.

૮. **ખભો** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મારા ખભામાં કોઈ જ તકલીફ નથી.
- ☐ મારો ખભા જકડાય ગયેલા છે પરંતુ મારી પ્રવૃત્તિ તથા શક્તિમાં કોઈજ અસર થતી નથી.
- ☐ મારા ખભાનાં દુખાવા તથા નબળાઈ ને કારણે મારે કાર્ય/શોખને બદલવો પડયો છે.
- ☐ મારા ખભાની તકલીફને કારણે હુ કાર્ય/શોખ કરી શકતો નથી.

૯. **સ્વાદ** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ હું હંમેશાની માફક ખોરાક નો સ્વાદ માણી શકુ છું.
- ☐ હું લગભગ બધા જ ખોરાક નો સ્વાદ માણી શકુ છું.
- ☐ હું અમુક ખોરાક નો સ્વાદ માણી શકુ છું.
- ☐ હું કોઈપણ ખોરાક નો સ્વાદ માણી શકતો નથી.

૧૦. **લાળરસ** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મારામાં લાળરસની માત્રા સામાન્ય છે.
- ☐ મારામાં લાળરસ સામાન્ય કરતાં ઓછું છે, પરંતુ તે પુરતુ છે.
- ☐ મારામાં લાળરસ ની માત્રા ખુબજ ઓછી રહે છે.
- ☐ મારામાં બીલકુલ લાળરસ નથી.

૧૧. **મનોસ્થિતી** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ મારી મનોસ્થિતી ઉત્તમ છે અને તેના પર કેન્સરનો પ્રભાવ નથી.
- ☐ મારી મનોસ્થિતી સારી છે પણ કોઈક વાર કેન્સરથી પ્રભાવિત થાય છે.
- ☐ હું કેન્સરને કારણે સારી મનોસ્થિતીમાં પણ નથી કે હતાશ પણ નથી.
- ☐ હું કેન્સરને કારણે હતાશ રહું છું.
- ☐ હું કેન્સરને કારણે ખુબજ હતાશ રહું છું.

૧૨. **ચિંતીત** (કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ હું મારા કેન્સર વિશે ચિંતીત નથી.
- ☐ હું મારા કેન્સર વિશે થોડો ચિંતીત છું.
- ☐ હું મારા કેન્સર વિશે ચિંતીત છું.
- ☐ હું મારા કેન્સર વિશે ખુબજ ચિંતીત છું.

છેલ્લા સાત દિવસો દરમ્યાન તમારા માટે કયા મુદ્દા મહત્વના હતા?
(વધુમાં વધુ ત્રણ ખાનામાં ખરાની નિશાની કરો ☑)

☐ દુખાવો	☐ ગળવું	☐ સ્વાદ
☐ દેખાવ	☐ ચાવવું	☐ લાળરસ
☐ પ્રવૃત્તિ	☐ વાચા	☐ મનોસ્થિતી
☐ મનોરંજન	☐ ખભો	☐ અસ્વસ્થ

સામાન્ય પ્રશ્નોત્તરીઃ

પ્રશ્ન: તમને કેન્સર થયુ તે અગાઉના એક મહિનાની સરખામણીમાં, તમે તમારા સ્વાસ્થ્યને સંબધિત જીવનની ગુણવત્તાને કેવી રીતે આંકશો?
(કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ ઘણું સારું
- ☐ થોડુ ઘણું સારું
- ☐ સરખું જ
- ☐ થોડુ ઘણું ખરાબ
- ☐ અત્યંત ખરાબ

પ્રશ્ન: છેલ્લા સાત દિવસો દરમ્યાનની તમારી સ્વાસ્થ્ય વિષયક જીવનની ગુણવત્તાની સામાન્ય માહિતી આપો
(કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ શ્રેષ્ઠ
- ☐ ખુબજ સારું
- ☐ સારું
- ☐ મધ્યમ
- ☐ નબળું
- ☐ વધું નબળું

પ્રશ્ન: એકદરે જીવનની ગુણવત્તામાં ફક્ત માનસિક અને શારિરીક સ્વાસ્થયનો જ સમાવેશ થતો નથી પરંતુ અન્ય પરીબળો જેવાકે કુટુંબ, મિત્રો, આધ્યાત્મીક અને વ્યક્તિગત મનોરંજનની પ્રવૃત્તિઓ પણ જીવન માણવા માટે વધુ મહત્વનો ભાગ ભજવે છે. આ તમામ મુદ્દાઓને ધ્યાનમાં રાખી ને, છેલ્લા સાત દીવસોમાં તમારા અંગત જીવન પર કેવો પ્રભાવ થયો છે અને તેને તમે કેવી રીતે આંકશો?
(કોઈ પણ એક ખાનામાં ખરાની નિશાની કરો ☑)

- ☐ શ્રેષ્ઠ
- ☐ ખુબજ સારું
- ☐ સારું
- ☐ મધ્યમ
- ☐ નબળું
- ☐ વધું નબળું

તમારી જીવનની ગુણવત્તાને લગતા મહત્વના અન્ય કેટલાક મુદ્દાઓ (તબીબી અને બિન-તબીબી) કે જેને અમે પ્રશ્નોત્તરીમાં આવરી લીધેલ ન હોય તેનુ તમે વર્ણન કરી શકો છો (જરૂર લાગે તો વધારાનું પાનું પણ લગાવી શકો છો.)

नाम:_____

तारीख: _____

वॉशिंग्टन विद्यापीठ की क्वालिटी ऑफ लाईफ प्रश्नावली
(UW-QOL)

यह प्रश्नावली आपके स्वास्थ्य और क्वालिटी ऑफ लाइफ के बारे में है। हम जानना चाहते हैं कि **पिछले सात दिन** में आपकी तबियत कैसी रही।

1. **दर्द.** (कृपया सही उत्तर बॉक्स ☑ में टिक करें)
   - □ मुझे बिल्कुल भी दर्द नहीं है।
   - □ हल्का सा दर्द है पर दवाई की जरूरत नहीं है।
   - □ मुझे थोडा दर्द है - नियमित दवाई की जरूरत है (कोडीव या अन्य दर्द निवारक)
   - □ मुझे बहुत तेज दर्द है जो सिर्फ नारकोटिक से कंट्रोल में आता है।
   - □ मुझे बहुत तेज दर्द है जो किसी नारकोटिक से कंट्रोल में नहीं आता है।

2. **रूप** (कृपया सही उत्तर बॉक्स ☑ में टिक करें)
   - □ मेरे बाहरी रूप में कोई बदलाव नहीं है।
   - □ मेरे बाहरी रूप का बदलाव बहुत ही आंशिक है।
   - □ मुझे अपना बाहरी रूप का बदलाव परेशान करता है पर मैं व्यस्त रहता हूँ।
   - □ मुझे अपना रूप खंडित लगता है और इसलिए मैं अपना काम काज सीमित रूप से करता हूँ।
   - □ मैं अपने बाहरी रूप के कारण लोगों के साथ नहीं रह सकता।

3. **एक्टिविटी/कार्यशीलता** (कृपया सही उत्तर बॉक्स ☑ में टिक करें):
   - □ मैं उतना ही एक्टिव हूँ जितना पहले था।
   - □ कभी ऐसा होता है जब मैं पहले जैसे एक्टिव नहीं होता, पर ऐसा कम होता है।
   - □ मैं अक्सर थक जाता हूँ और अपनी कार्यशैली को कम करता हूँ पर फिर भी मैं बाहर जाता हूँ।
   - □ मैा बाहर नहीं जाता क्योंकि मुझमें ताकत नहीं हैं।
   - □ मैं अक्सर लेटता हूँ या कुर्सी पर बैठता हूँ और घर के बाहर नहीं जाता।

4. **मनोरंजन** (कृपया सही उत्तर बॉक्स ☑ में टिक करें):
   - □ घर या बाहर मुझे मनोरंजन के हर क्षण में मजा आता है।
   - □ कुछ चीजें ऐसी हैं जो मैं कर नहीं सकता पर फिर भी बाहर जाकर जीवन में मजा लेता हूँ।
   - □ अक्सर मैं चाहता हूँ कि मैं अधिक बाहर जा सकूँ पर मैं कर नहीं पाता।
   - □ मेरे हर काम में मुझे अनेक बाधा आती है सो मैं अक्सर घर में रहकर टीवी देखता हूँ।
   - □ मैं कुछ भी ऐसा नहीं कर पाता जिसमें मुझे मजा आये।

5. **निगलना** (कृपया सही उत्तर बॉक्स ☑ में टिक करें):
   - □ मैं पहले जैसे निगल सकता हूँ।
   - □ मैं कुछ सोलिड खाना नहीं खा पाता।
   - □ मैं सिर्फ तरल खाने के पदार्थ निगल सकता हूँ।
   - □ मैं बिलकुल निगल नहीं सकता क्योंकि वो गलत तरु चला जाता है और मैं चोक हो जाता हूँ।

6. **चबाना** (कृपया सही उत्तर बॉक्स ☑ में टिक करें):
   - □ मैं पहले जैसे चबा सकता हूँ।
   - □ मैं सॉफ्ट सोलिड खाना चबा सकता हूँ पर हर तरह का खाना नहीं चबा सकता ।
   - □ मैं सॉफ्ट सोलिड खाना भी नहीं चबा सकता हूँ।

7. **बोलचाल**: (कृपया सब प्रश्नों का सही उत्तर बॉक्स ☑ में टिक कर)
   - □ मेरी बोलचाल पहले की तरह है।
   - □ मुझे कुछ शब्द कहने में तकलीफ होती है पर लोग मुझे फोन पर समझ लेते हैं।
   - □ सिर्फ मेरे परिवार और मित्र मेरी बातचीत समझते हैं।
   - □ मुझे कोई भी बिल्कुल नहीं समझ पाता।

8. **कंधा** : (कृपया सही उत्तर बॉक्स ☑ में टिक करें)
   - □ मुझे अपने कंधे में कोई तकलीफ नहीं है।
   - □ मेरा कंधा थोडा कडा है पर इससे मेरे काम काज या शक्ति में कोई फर्क नहीं पडा है।
   - □ कंधे में दर्द या कमजोरी के कारण मुझे अपना काम बदलना पडा है।
   - □ मैं कंधे की तकलीफ के कारण कोई काम नहीं कर पाता ।

9. **स्वाद** : **(**कृपया सही उत्तर बॉक्स ☑ में टिक करें**)**

□ मुझे खाने का स्वाद नार्मल आता है।

□ ज्यादातर खाने की चीजों का स्वाद नार्मल आता है।

□ मैं कुछ चीजें का स्वाद पाता हूँ।

□ मुझे खाने का स्वाद नहीं पता चलता ।

10. **थूक** : **(**कृपया सही उत्तर बॉक्स ☑ में टिक करें**)**

□ मेरे थूक का गाढापन नार्मल है।

□ मेरे मुँह में कम थूक है पर वो नार्मल है।

□ मेरे मुँह में बहुत कम थूक है।

□ मेरा मुँह एकदम सूखा है।

11. **मन:स्थिति**: **(**कृपया सही उत्तर बॉक्स ☑ में टिक करें**)**

□ मेरी मन:स्थिति उत्तम तथा मेरे कैंसर से अप्रभावित है।

□ मेरी मन:स्थिति सामान्यत: अच्छी सहती है और कभी कबार मेरे कैंसर से प्रभावित होता है।

□ मैं मेरे कैंसर को लेकर न अच्छी मन:स्थिति में हूँ और न ही उदास हूँ।

□ मैं मेरे कैसर के बारे में थोडा उदास हूँ।

□ मैं मेरे कैसर के बारे में बहुत उदास हूँ।

12. **चिन्ता : (**कृपया सही उत्तर बॉक्स ☑ में टिक करें**)**

□ मैं मेरे कैसर के बारे में चिन्तित नहीं हूँ।

□ मैं मेरे कैसर के बारे में थोडा चिन्तित हूँ।

□ मैं मेरे कैसर के बारे में चिन्तित हूँ।

□ मैं मेरे कैसर के बारे में बहुत चिन्तित हूँ।

<u>पिछले सात दिन</u> में आपके लिए क्या सबसे विशेष महत्व का था ? **(**किसी भीं तिन बॉक्स ☑ में टिक करें**)**

□ दर्द	□ निगलना	□ स्वाद
□ रूप	□ चबाना	□ थूक
□ कार्यशीलता	□ बातचीत	□ मन:स्थिति
□ मौजमस्ती	□ कंधे	□ चिन्ता

आम प्रश्न

कैंसर होने के एक महीने पहले और आज में आप आपके स्वास्थ्य में क्या फर्क लगता है? (कृपया सब प्रश्नों का सही उत्तर बॉक्स ☑ में टिक करें)

□ पहले से बहुत अच्छा
□ थोडा बेहतर
□ करीब करीब वैसे ही
□ पहले से बदतर
□ बहुत खराब

स्वास्थ्य और क्वालिटी ऑफ लाइफ का पिछले सात दिन का सन्तुलन कैसा रहा है? (कृपया सब प्रश्नों का सही उत्तर बॉक्स ☑ में टिक करें)

□ बहुत बढिया
□ बहुत अच्छा
□ अच्छा
□ ठीक ठीक
□ कोई खास नहीं
□ बहुत खराब

समग्र रूप से क्वालिटी ऑफ लाइफ आपके शारीरिक और मानसिक स्वास्थ्य के अलावा परिवार, मित्र, आस्मिक और मनोरंजन के कार्यक्रम पर भी निर्धारित हैं। इनसे आप जीवन का मजा ले सकते हैं। हर वो चीज आपको सुख देती है उसे ध्यान में रखते हुए पिछले सात दिनों में **समग्र रूप से आपकी क्वालिटी ऑफ लाइफ** कैसी रही ? (कृपया सही उत्तर बॉक्स ☑ में टिक करें)

□ बहुत बढिया
□ बहुत अच्छा
□ अच्छा
□ ठीक ठीक
□ कोई खास नहीं
□ बहुत खराब

ऐसे कुछ प्रश्न होंगे जो इस प्रश्नावली में नहीं है पर वो आपको अपने जीवन को संपूर्ण रूप से जानने के लिए जरूरी है। कृपया उसके बारे में लिखें।

QED Clinical Services India Pvt Ltd
C-408, Titanium Square
Thaltej Cross Roads
S. G. Highway, Thaltej
Ahmedabad – 380054
Gujarat, India
Phone: +91 79 4032 4300
Fax: +91 79 4032 4301
Website: www.qed-clinical.com

21 Feb 2014

Drasty Vora
Institute of Pharmacy
Nirma University
Ahmedabad

Subject: Summer Training and Project Work

Dear Drasty,

With reference to your application and subsequent face to face meeting, we are pleased to confirm that; you are selected for summer training and project work at QED Clinical Services India Pvt Ltd**.,** Ahmedabad**.**

A per our discussion with Institute representative; Mr. Tushar Patel (Manager, Corporate Relations, Nirma University), we understand that; you will join us for summer training in mid May 2014 and then will continue your project work with us till Apr 2015. The total expected duration of your internship with QED is about one year.

Your internship with QED will include training/orientation in clinical research filed and hands on experience on various clinical trials related activities. We will also provide support and suggestions for your project work in consultation with your guide/institute.

You are expected to report at following address for your summer training and project work.

QED Clinical Services India Pvt Ltd
C-408, Titanium Square
Thaltej Cross Roads
S. G. Highway, Thaltej
Ahmedabad – 380054
Gujarat, India

Contact person: 1. Ali Sajjad Bohra. 2. Swadhin Khawas

Congratulations once again and we are looking forward to have you at QED.

Kind Regards

_____
Ali Sajjad Bohra
Country head and Director, Operations

Turnitin Originality Report

PML by Drasty Vora

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Marshall, L. J., M. W. Ferenczy, E. L. Daley, P. N. Jensen, C. F. Ryschkewitsch, and E. O. Major. "Lymphocyte Gene Expression and JC Virus Noncoding Control Region Sequences Are Linked with the Risk of Progressive Multifocal Leukoencephalopathy", Journal of Virology, 2014.

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Submitted to Milford High School on 2014-11-17

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Belser, Jessica A. Blixt, Ola Chen, Li-M. "Contemporary North American influenza H7 viruses possess human receptor specificity: implications fo", Proceedings of the National Academy of S, May 27 2008 Issue

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Mark T M Roberts. "AIDS-Associated Progressive Multifocal Leukoencephalopathy", CNS Drugs, 2005

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A Sami Saribaк. "JC virus-induced progressive multifocal leukoencephalopathy", Future Virology, 05/2010

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18 < 1% match (publications)

Julie Roskopf. "Pharmacotherapeutic Options for the Management of Human Polyomaviruses", Advances in Experimental Medicine and Biology, 2006

paper text:

INTRODUCTION Orphan diseases are the ones which affect fewer numbers of patients. The definition of orphan diseases varies from country to country. As per USA,

> 12**An orphan disease is defined as a condition that affects fewer than 200,000 people nationwide.1**

It is important to note that

> 680 of rare diseases have identified genetic origins whilst others are the result of infections (bacterial or viral), allergies and environmental causes, or are degenerative and proliferative. 2 50% of rare diseases touch/ affect children. 3 Orphan disease is

defined in different aspects globally as follows: Country U.S Orphan Disease definition A

> 2drug developed under the Orphan Drug Act, anuary 1983 is an orphan drug in US market. A

disease that affects fewer than 200,000 people or is

> 2of low prevalence (less than 5 per 10,000 in the community)

is termed as an Orphan Disease in US.

> 2Europe A disease or disorder that affects fewer than 5 in 10,000 citizens.

> 2 apan Any disease with fewer than 50,000 prevalent cases (0.4).

Australia Any disease orconditions affecting

> 1fewer than 2,000 individuals at any one time is termed as orphan disease

in Australia.

> 2Canada Canada has no official orphan disease status; however, based on international standards, it could be defined as diseases with a potential patient population around 3,300.

Asian Perspective of Rare Disease

> 2India The need for an orphan act is evident from the initiative by the Indian Pharmacists and the Government to implement Laws, which would

strengthen the infrastructure of health services **and provide relief to numerous rare disease sufferers throughout the country. A group of pharmacologists at a conference held by Indian Drugs Manufactures Association in 2001 requested Indian Government to** implement **Orphan Drug Act in India. Taiwan The official definition of rare disorders is a disease if it is prevalent in 1:10,000 people. On February 9, 2000, Taiwan's Legislative uan implemented the Rare Disease and Orphan Drug Act to improve the diagnosis, treatment, and prevention of rare diseases in Taiwan.**

Korea If

1**less than 20,000 people** are affected **from any disease or** if **there is no** treatment **available for** that **disease,** than it **is** termed **as** Rare **/Orphan disease**

in Korea. Table 2.1 Definition of Orphan Disease globally An Overview of Drug Discovery Process:- Drug discovery has always been an interesting field with multiple challenges yet with rewarding and satisfying outcomes. A typical drug discovery process would take around 10-15 years of time to bring a new drug to the market; and consumes around 1 billion US dollars or sometimes even more specially with biologicals and specialty medicines. However, the successes of the drugs developed are not guaranteed. It is estimated that 90% of all drugs entering various clinical trials are discontinued, more often due to issues associated with efficacy than safety. Fig: - 2.1 overview of Traditional drug development process Drug development process in orphan diseases is generally slow due to limited information available on the disease and scarcity of the patients and also due to several other operational and cost factors. Also there are over 7000 rare diseases known in this world. The clinical development and designation for these rare diseases drugs is far different compared to traditional diseases and their drugs as shown in figure below. The major challenges associated with orphan drug development are less number of affected patients, high cost, unknown aetiology of diseases, limited information etc. Thus orphan drug development is really a challenging and very difficult task. Fig: -2.2An overview of Orphan drug development and designation process. Taking the very fact into consideration, a new field that has come into existence is Drug Repositioning/Repurposing. By definition,

7**Drug repositioning (also known as Drug repurposing, Drug re-profiling, Therapeutic switching and Drug re-tasking) is the application of known drugs and compounds to new indications (i.e., new diseases).** [4] **Drug**

repurposing offers to explore the existing knowledge on drugs, diseases and targets and helps us to find a novel use of an already available compound or drug lead for the development of new and better therapies. Since drug repurposing offers a relatively low-risk, recovering losses, save both money and time, most companies are now heading for reprofiling of existing drugs. It is because of this reason drug reprofiling is becoming increasingly popular in the industry. A few older instance of drug repurposing are like Sildenafil, a generic drug, initially used for Angina was later repositioned and used for Erectile Dysfunction and Pulmonary Hypertension. Aspirin was originally meant for treating pain, is now prescribed as a vasodilator

for reducing the risk of heart attack and strokes. Minoxidil, a generic drug made for hypertension and manufactured by Pharmacia & Upjohn in Sweden was repositioned by Pfizer for Rogaine, the drugs trade name, currently used for the treatment of hair loss. Repurposing efforts in orphan disease areas can also prove to be very valuable in bringing newer medication to rare disease patients who are in desperate need of medications for the management of their diseases. Table:-2.2 Examples of some Repositioned Drugs in various diseases are as follows: - [5] Drug Original Indication New Indication

5**Aspirin Inflammation, pain** Anti-platelet **Bromocriptine Parkinson's Disease Diabetes Mellitus Finasteride Prostate Hyperplasia Hair loss Gemcitabine Viral** Infection **Cancer Methotrexate Cancer Psoriasis,** Arthritis **Rheumatoid Minoxidil Hypertension Hair loss Raloxifene Cancer Osteoporosis Thalidomide Morning Sickness Leprosy, Multiple Myeloma**

Similarly, Examples of Repositioned Drugs for Orphan disease is as follows:- Drug Original Indication Orphan Indication Ciprofloxacin Anti-infective Cystic Fibrosis Mifepristone Abortifacient. Hypercortisolism Miltefosine Antifungal and Cutaneous T-cell Antiprotozoal Lymphoma

1**Ascorbic acid** Scurvy **Charcot-Marie-Tooth disease type 1A Ketoconazole Anti-** infective **Treatment of Cushing syndrome Sialic acid** Acne **Treatment of hereditary inclusion body myopathy**

Amphotericin B Fungal Infection Leishmaniasis Table 2.3 Examples of Repositioned drugs in Orphan Diseases Various methods utilised for Drug Repositioning are as follows:-

5**1) Drug Focus** Approach: - **Structural features of molecules already approved for particular indications can help to identify active compounds that were originally developed for different indications.** Advanced softwares **can perform similarity searches and produce advanced QSAR models based on** the collections **of** bioactive compounds in **the**

5**world including compounds from patents and articles registered in databases, and other sources.** Drug **Focus**

1**approach can be** done by **two ways**ñOn-targetò **and**ñOff-targetò **In**ñon-targetò **approach, drug's pharmacological mechanism is already known that will be applied to the new indication. It can be possible that same mechanism of drug can treat other several diseases (Pfizer's Sildenafil having mechanism of vasodilation but it was unsuccessful in hypertension but it was**

successfully used in male erectile dysfunction and by applying same mechanism it was designated for pulmonary arterial hypertension a rare disease) andñoff-targetòmeans looking or identifying a newer mechanism of existing molecule and approaching it. It is more innovative approach for drug repurposing.

1A molecule is taken and extensive literature search is carried out for its published work and all possible mechanism will be identified and then after identifying newer possible mechanism and specific targets screening will be done and result will be narrow down to a limit till a molecule can be effective in targeting certain type of diseases. Off target approach require more time for drug repurposing as there will be new possible mechanism is going to identify so there will be new clinical trial is required. An existing molecule is already been used for a particular disease so complete data

of a molecule will be available. 2) Disease Focus:-Experimental data related to disease

5or knowledge on how drugs modulate phenotypes related to disease (e.g. Known from their side effects) are checked in disease

focus approach.

1An orphan disease with unknown pathophysiology, aetiology and unmet medical need will be approached and existing drugs will be targeted for that disease and effectiveness of drug will be checked for that particular disease.

Orphan drug development benefits: In

1past, Pharmaceutical companies had very limited interest in orphan drug development due to heavy investments and limited returns. To promote research in orphan areas, health agencies have

brought some unique advantages which have attracted biopharmaceutical companies to start working in the orphan drug areas. In our thesis we are targeting repositioning of drug in an orphan disease named Progressive Multifocal Leucoencephalopathy, therefore it is important to know that for the orphan drug development health agencies has come up with many benefits which are listed as below:- ? Designation is

2granted based on prevalence of disease in the population of less than

200,000 people (approximately 0.1)

and 5 in 10,000.This criteria of orphan designation is achieved for PML from its prevalence data. ? ? ? ? ?

2**Protocol assistance to design research protocols.** Funding grants **for clinical research**

to support development.

1**Tax credits for clinical research.** Market exclusivity. **Orphan** drug **market exclusivity**

of different countries is as follows:-

2**Countries Market Exclusivity** US **7 years Europe 10 years apan 10 years Korea 6 years Singapore 10 years Taiwan 10 years**

Table:-2.4 Orphan Drug Market Exclusivity of Different Countries Aim and Objectives: There are various reasons for utilising drug repositioning/repurposing efforts for orphan diseases. Few of the logical reasons are as follows: ?

1**There are over 7000 orphan diseases out of which only 300-400 have established medications for treatment. Hence, there is an unmet medical need to develop drugs for the management of orphan diseases. ? Traditional drug development approaches would take over 500 years to find treatment for all these diseases. ? Global slowdown, drying pipelines, increased R D costs, expiring patents of block- buster drugs and cost pressure deters pharma companies to invest large sums for the development of orphan drugs.**

?

1**Repurposing/Repositioning of existing drugs with known pharmacology/toxicology for the treatment of orphan diseases is most appropriate, less time consuming and cost effective approach. Keeping** the above mentioned **facts in mind, we** planned **to** study **the** repurposing **of** drug for **the**

orphan disease progressive multifocal Leucoencephalopathy.

1Aim: Repurposing/Repositioning the drugs for the management of orphan

disease-Progressive Multifocal Leucoencephalopathy (PML) Objectives: ?

1Review already existing drugs for their suitability for the treatment of Progressive Multifocal Leucoencephalopathy. ? Identify one

potential medication for Orphan designation in PML. REVIEW OF LITERATURE

16Progressive Multifocal Leucoencephalopathy (PML) PML is a rare infection of CNS that damages the

white matter of the brain7. The inflammation

18of the white matter of the brain

at multiple locations is termed as PML. It

11is a rare infection which damages the Myelin Sheath that covers and protects Nerves in the white matter of the

brain8. Although it is a rare disease but serious infection may lead to severe disability or death.9 PML is caused by a virus known as JC virus (John cunninghgum Virus-named from the initials of the patient from whose tissues the virus was first successfully cultured)

17Majority of the adult Population is infected with the JC virus

but do not develop the disorder. The virus activates only in certain conditions such as weakened immune system or due to certain immunosuppressant drugs.8 PML is a rare disorder, but it can occur in a various types of patients such as follows:- ? AIDS and HIV patients ? Cancer patients such as Lymphoma and Leukaemia ? Chronic steroid therapy to suppress Immune system. ? Transplantation of organs ? Immunosuppressive conditions. ? Certain therapeutic treatments affecting the immune system such as medicines used to prevent organ transplant rejection, or to treat Multiple Sclerosis, Rheumatoid Arthritis, and PML is aggravated as their side-effects.7 Symptoms of PML are as follows: - ? Loss of co-ordination. ? Loss of language ability ? Seizures ? Memory loss ? Vision Problems ? Weakness of the legs and arms ? Personality changes ? Headaches8

4Symptoms typical of PML are the result of demyelination – often in multiple areas of the brain – caused by the viral infection.

4**Symptoms vary and increase in severity as disease progresses. PML frequently presents as hemiparesis, ataxia, cognitive or** behavioural **changes, or visual disturbances. It is important to note that diagnostic criteria should be considered in the context of primary indications and therapeutic areas. Neither fever nor optic nerve involvement is a feature of PML, and spinal cord disease is rarely associated with it. Symptoms**

begin gradually and usually worsen progressively and severe disability or death may often result. Symptoms may differ depending on the part of the brain affected. If PML is

13**left unmanaged, the mortality rate is 30-50 within the first three months of diagnosis.**

Even if death does not result, it is likely that some significant damage will be permanent.8

3**Risk Factors: - PML is likely caused by a combination of factors. Risk factors include the presence of pathogenic CV and an altered or weakened immune system; they may also include genetic or environmental risk factors.**

1. Presence of Pathogenic JC Virus. Mostly Majority

3**of the adult population is** likely **to be infected with CV,**

only the presence of altered virus is seen in PML patients. Thus presence of altered virus having

3**mutations in the non- coding** region **or the VP1** envelop **protein is considered as a risk factor for PML.**

ELISA Test enables us to detect anti-JCV antibodies indicating past infection. This assay can be used in patients to identify the

3**higher risk for PML** in patients **because of CV infection. However, it cannot distinguish between antibody against wild-type and mutated virus. Other methods to detect CV infection may not be sufficient because of poor sensitivity (assays for CV DNA in blood) or intermittent (viremia or) viruria (assays for viral DNA).**

9 2. Weakened Immune System

> 3**Compromised immune system** enables **infection and viral replication in the brain** which **is one of the key risk factors for PML.** Aggravating **factors**

which alters immune system and resulting in PML is as follows:- o o HIV-AIDS Lympho reticular

> 3**malignancies • Chronic Lymphocytic** Leukaemia Å**Hodgkin's disease • Non-Hodgkin's Lymphoma** o o **Systemic Lupus Erythematosus Treatment with certain immunosuppressive or immunomodulatory therapies in the context of: • Crohn's disease • Multiple Sclerosis • Oncology • Psoriasis • Rheumatoid Arthritis • Transplantation**

Also some drugs aggravates PML as a part of their side effects. The list of such drugs is as follows:- ? Rituximab ? Natalizumab ? Alemtuzumab ? Cyclophosmamide ? Prednisolone ? Mycofenolate mofetil ? Tacrolimus ? Dexamethasone[10] 3. Genetic Risk Factors

> 10**Naturally occurring CV sequence variation, together with drug treatment-induced** cellular **changes, may synergize to create an environment leading to an increased risk of PML. The**

> 3**rarity of PML in the general population suggests that additional factors may contribute to susceptibility in conjunction with viral mutation and immune suppression/modulation. It has been proposed that certain human genetic or environmental risk factors may increase susceptibility to PML; however, specific risk factors have not yet been identified.**

11 Diagnosis of PML is mainly done by two methods as follows:- 1. Brain Imaging Characteristic of PML.(MRI) Magnetic Resonance Imaging method is the mostly used and reliable technique to evaluate neurological status and progression of brain lesion. Conditions Explanation of Symptoms Technique for Detection Brain Imaging Characteristics Unifocal or Multifocal Lesions MRI Table: - 3.1 Brain Imaging characteristic of PML

> 4**PML is associated with Unifocal or multifocal lesions, which may be detected using MRI. The lesions most commonly appear in the subcortical white matter or cerebellar hemispheres**

and are hyper intense

4**on T2-weighted images and/or FLAIR (fluid-attenuated inversion recovery) sequences, and** hypo intense **on T1-weighted images. In rare cases, the presentation of PML may be a progressive cerebellar disease, in which case an MRI would only display cerebellar atrophy, or a cortical** presentation; **for this reason, clinical vigilance is crucial to the early identification of PML-related signs and symptoms.**

11 Figure 3.1 Features and Classification of PML Figure:-3.2 PML Disease Progression pattern 2.

4**Detection of C virus DNA in the Cerebrospinal Fluid or Evidence of CV Infection on a Brain Biopsy.**

Finding of JCV DNA in brain biopsy is considered as a final diagnosis of PML. JCV DNA is not detectable in the early stages of the disease and additional biopsy should be done. Also expertise in JCV detection is needed due to the complexity by virus mutations. Highly sensitive and quantitative PCR test is suggested.12,13 Incidence and Prevalence of PML: - Institute of Pharmacy, Nirma University Figure:-3.3 Prevalence of PML in Europe Page 16 28 6 48 1 4 9 9 NO.OF CASES IN EUROPE 515 163 2 1112 278 60 1 277 1 230 out from PubMed FROM 1960-2014.14-61 specific journal of different countries and search engine Google. Total of 3271 articles were screened ñProgressive Multifocal Leucoencephalopathyò search was carried out from PubMed, Science Direct,

1**Methodology for finding prevalence of** PML: - **literature search was carried out by putting Mesh term**

carried out.

1**As such no proper data were available regarding the prevalence of** PML **extensive literature search was**

Chapter 2 [Pick the date] NO.OF CASES IN ASIA-PACIFIC 99 22 5 5 1 2 1 AUSTRALIA CHINA INDIA JAPAN KOREA SINGAPORE THAILAND Figure:-3.4 Prevalence of PML in Asia-Pacific NO.OF CASES IN AFRICA AND MIDDLE-EAST 28 14 1 SOUTH-AFRICA ISRAEL(MIDDLE-EAST) (MIDDLE-EAST) Figure:-3.5 Prevalence of PML in Africa and Middle -East Institute of Pharmacy, Nirma University of PML cases. Page 18 The total number of cases was found to be 4899. U.S and Europe was found to have the highest number Figure:-3.6 Prevalence of PML in USA 1 1 3 2 1 1 1 1 463 36 61 55 17 157 1 19 2 9 242 1 47 1 1 1 205 4 5 12 3 1 35 1 1 NO.OF CASES IN USA 1 1 2 11 25 1 32 13 2 285 212 105 118 Chapter 2 [Pick the date] Mechanism/Pathogenesis of PML. JC Virus selectively targets cells in the kidney and brain. JCV requires sialic acids to attach to host cells and initiate infection, and JCV demonstrates specificity for the oligosaccharide lacto series tetra saccharide c (LSTc) with an Ŭ2,6-linked sialic acid. Following viral attachment, JCPyV entry is facilitated by the 5-hydroxytryptamine (5-HT) 2 family of serotonin receptors via clathrin-dependent endocytosis. JCPyV then undergoes retrograde transport to the endoplasmic reticulum

(ER) where viral disassembly begins and infection occurs.62,63 Treatment:- There is no reliable treatment for PML till date. Many anti-viral therapies such as cidofovir and mefloquine have been tried for the management of PML. However, the results were not encouraging. Various mechanisms have been studied by the scientists to fight against PML such as:- 1) Drugs stimulating the immune system (interleukin-2, Alpha Interferon and Beta Interferon) 2) Drugs that block viral entry into cells (chlorpromazine, Risperdone, mirtazapine) and 3) Drugs that target the replication of the virus (cidofovir, CMX001, mefloquine, Cytarabine and Topotecan). Imatinib and IL-7 is an orphan designated drug for the treatment of PML. Thus to target PML two approaches were taken into consideration from the mechanism as follows:- 1) To inhibit or bind sialic acid to hinder attachment of virus with the host cells. 2) To target entry of virus using 5HT2 Antagonist. Certain plant lectins such as

8**a lectin from the seeds of Maackia amurensis**

binds sialic acid and inhibits cell growth and migration

8.**Mistletoe lectin (viscumin) binds proteins containing α2, 3-sialic acid, has undergone successful clinical trials, and is widely used to treat melanoma in Europe.**

High sialic acid leads to cancer as it creates

9**negative charge on cell membranes** which **creates repulsion between cells and** thus produces cancer. **These**

lectins are widely used to treat cancer. These Lectins can be used for treating PML as it hinders sialic acid thus the virus will not find sialic acid and infection will not initiate.64 Selective strategies to interfere with sialic acid synthesis might offer a good approach to treat progressive multifocal Leucoencephalopathy. Also P-3F (ax)-Neu5Ac is a fluorinated sialic acid analog and blocks the synthesis of sialic acid by depleting

15**alpha 2, 3 and alpha 2, 6 linked sialic acids.**

65 Also,

9**anti-influenza drugs** like **oseltamivir and anamivir are sialic acid analogs that** interferes **with** the **release of newly generated viruses by**

cleavage of sialic acids. Thus these drugs can also be used for treating PML. Several compounds were screened to check the structure of these viruses and it was reported that Gallic acid possesses similar chemical space as sialic acid to bind the JC virus. Even Gallic acid possesses good blood brain barrier crossing capacity.66 The efficacy of above mentioned compounds such as various lectins, Oseltamivir and Zanamivir were assessed by thorough literature study and following end results were seen:- Table:-3.2

Compounds screened and their drawbacks Name of compounds Drawbacks Lectins from Maackia Amurensis and Mistletoe Lectins. PML has affinity

> 14**for Alpha 2,** 6 **-linked sialic acids**

whereas these lectins have affinities

> 14**for Alpha 2, 3 -linked sialic acids.** Thus **not** applicable **in**

PML. P-3F(ax)-Neu5Ac - a fluorinated sialic acid Unknown compound and no full proof evidences available Oseltamivir and Zanamivir Cannot cross BBB so not applicable for PML Gallic acid analogs and Terguride Unknown compound and no related information available.(Evidences were not available for Terguride) Thus due to above discrepancies the concept of targeting sialic acids will not work so another approach is taken into account. Terguride is also a proposed drug and can be used in PML due to the following reasons:- Terguride acts as 5HT2 A/ B Antagonist and can also cross blood brain barrier. Terguride also elevates dopamine levels which improves mood related disorders and results in euphoria or ecstasy. Also Terguride is Orphan Designated drug for pulmonary arterial hypertension and Systemic Sclerosis. Also it is very old molecule so toxicity and other datas such as teratogenicity etc. are available and is comparatively safe. Thus Terguride can be employed for the treatment of PML. Drug designated for treatment of PML IL-7 is associated with Renal and Ocular Toxicity, Terguride has tolerable side-effects such as Confusional state and Hyponatremia. Thus Terguride can be used as a possible ray of hope for the treatment of PML. From Mechanism point of view Terguride can be employed for the treatment of PML, but clinical evidences and proof of using Terguride in PML is not available. Due to lack of sufficient evidences Terguride cannot be suggested for further work because without evidence confirmation about the proposed mechanism does not hold any value. Thus Terguride is not studied further for Progressive Multifocal Leucoencephalopathy. Reports and literature search have suggested use of 5HT2A receptor antagonists for the treatment of Progressive Multifocal Leucoencephalopathy. Also offline many serotonin antagonist drugs such as Mirtazapine, Risperdone, Olanzapine has been used and improvement in disease is reported. In certain case reports disease is cured completely. 5HT2 Receptors allows entry of virus so if 5HT2 receptor is blocked it will further stops the further progression of disease. Table:-3.3 list of drugs used offline for PML is as follows:- Sr. no Title Name of Drug No. of cases Reference 1 Mefloquine progressive improved multifocal Mefloquine 1 J Clin Neurosci. 2014 Oct; Leukoencephalopathy in a 21 (10):1661-4. Doi: patient with 10.1016/j.jocn.2013. immunoglobulin A 12.031. Epub 2014 nephropathy. May 27. 3 Progressive Multifocal Leukoencephalopathy with Immune Reconstitution Inflammatory Syndrome (PML-IRIS): two case reports of successful treatment with Mefloquine and a review of the literature. Mefloquine 2 Ann Acad Med Singapore. 2012 Dec; 41 (12):620-4. 4 Favourable outcome of progressive multifocal Leukoencephalopathy with Mefloquine treatment in combination with antiretroviral therapy in an HIV-infected patient. Mefloquine 1 Int J STD AIDS. 2012 Aug; 23 (8):603-5. Doi: 10.1258/ijsa.2012.01 1305. 5 Neuropharmacokinetic heterogeneity of Mefloquine in the treatment of progressive multifocal Leukoencephalopathy. Mefloquine 1 Intern Med. 2012; 51(16):2257; author reply 2259. Epub 2012 Aug 15. 7 Mefloquine improved progressive multifocal Leukoencephalopathy in a patient with systemic lupus erythematosus. Mefloquine 1 Intern Med. 2012; 51(10):1245-7. Epub 2012 May 15 8 Pharmacokinetic Mefloquine 1 Clin Neurol considerations in the repositioning of Mefloquine for treatment of progressive multifocal Leukoencephalopathy. Neurosurg. 2012 Oct; 114(8):1204-5. Doi: 10.1016/j.clineuro.2 012.02.046. Epub 2012 Mar 14. 10 Akinetic mutism caused by HIV-associated progressive multifocal Leucoencephalopathy was successfully treated with Mefloquine: a

serial multimodal MRI Study. Mefloquine 1 Intern Med. 2012; 51(2):205-9. Epub 2012 Jan 15. 12 Mefloquine treatment in a patient suffering from progressive multifocal Leucoencephalopathy after umbilical cord blood transplant. Mefloquine 1 Intern Med. 2010; 49(22):2509-13. Epub 2010 Nov 15. 13 Mefloquine in the treatment of progressive multifocal Leucoencephalopathy Mefloquine 1 J Neurol Neurosurg Psychiatry. 2011 Apr; 82(4):452-5. Doi: 10.1136/jnnp.2009.1 90652. Epub 2010 Jun 20. 17 Treatment schedules for 5- HT2A blocking in progressive multifocal Leucoencephalopathy using Risperidone or Ziprasidone. Risperidone Ziprasidone and 2 Bone Marrow Transplant. 2007 Jun; 39(12):811-2. Epub 2007 Apr 23. 18 Risperidone-induced reduction in JC viruria as a surrogate marker for efficacy against progressive multifocal Leucoencephalopathy and haemorrhagic cystitis. Risperidone 1 J Clin Virol. 2007 May; 39(1):63-4. Epub 2007 Apr 3 20 The atypical antipsychotic agentsÕ Ziprasidone [correction of Ziprasidone], Risperdone and olanzapine as treatment for and prophylaxis against progressive multifocal Leukoencephalopathy. Ziprasidone, Risperidone and Olanzapine 1 Med Hypotheses. 2005; 65(3):585-6. Above cases are drugs used offline in PML taken from PubMed articles by scrutinizing each cases. Apart from Terguride data of other 5HT2 Receptor antagonists are available and used offline. Case reports of single drugs and combination Drugs as listed in above table shows good results in PML. Institute of Pharmacy,BNeicramusaeUé n..iversity Page 25 ? It shows promising results in case Chapter 2 ÅNo strong case reports were found and cannot cross BBB. ÅIt rises immune system and thus cannot be used in transplantation patients. ÅMefloquine-Trial conducted but results were not promising. ÅCytarabine-shows bone marrow toxicity and trial report was not significant. Immunomo dulating drugs Mefloquine and cytarabine WHY MIRTAZAPINE???? PML [Pick the date] ÅCidofovir shows toxicity in cells of neural origin and cannot pass BBB. ÅWork had been done on CMX001 and shows good results invitro and some case reports. Cidofovir and CMX001 Risperidone and Topotecan ÅNo strong case reports and evidences found for both Risperidone and Topotecan. reports and combination therapy. Figure:-3.7 Presentation for why Mirtazapine as a drug of choice Screening of Individual Drugs:- 1. Immunomodulating drugs Interleukin-II an Immunomodulating drug and is responsible for the activation of Lymphocytes and is used in the treatment of specific forms of cancer. Three case reports of HIV patients along with PML showed positive responses when treated with IL-II. Other Immunomodulating drugs are Interferon alpha and beta. They interfere in replication of virus by activating macrophages and natural killer cells. A case control study in 1999 showed report on 53 HIV patients along with PML from which 21 were treated with Interferon alpha, showed increased survival of patients. Another study conducted in 2001 having 97 HIV patients from which 36 were treated with INF- alpha, showed no remarkable advantage over non-treated patients. One single case-study was found in which the patient having HIV was treated for four months with INF-beta but Brain lesions showed no significant improvement and patient died within four months. Thus Immunomodulating drugs are not much efficacious in PML as they lack BBB crossing capacity.67,68 2. Cidofovir According to the case reports and clinical studies from 1995 to July 2000, use of cidofovir for PML was reviewed. Most case reports suggests use of cidofovir to be effective in the treatment of PML. Cidofovir can be the most reliable treatment option for PML in HIV infected patients who fail to improve with HAART. A case report of HIV patient treated with cidofovir for PML was reported. In 1998, a case was reported in which patient was having PML with HIV, where cidofovir in addition to HAART was given to the patient and also showed improvement in Brain lesions. In the following years 10 different case reports were issued, 7 patients among them showed response to the treatment. The three patients that did not respond to the treatment were reported in one article and were not HIV infected, two had chronic lymphatic leukaemia and one had multiple myeloma. 6 out of the 7 other patients were HIV infected, one had chronic lymphatic leukaemia. Moreover, for all three non-responsive patients the diagnoses was based on both MRI scans and the detection of JCV DNA in the Cerebrospinal fluid by PCR. Nevertheless only one patient among three post mortem examination was performed and PML was detected. On top of those case reports, 6 case control studies were performed. In 2008 Di Luca et al. combined the results of these 8 case control studies in which

AIDS-related PML patients received combination antiretroviral therapy with or without cidofovir. It was concluded that there was no remarkable change in PML related mortality. Moreover, cidofovir showed some toxicity in cells of neural origin. It was not clearly distinguished that improvement is seen because of cidofovir or due to HAART therapy in HIV patients. Cidofovir cannot cross BBB and thus its derivative was prepared for more efficacy and BBB crossing capacities. 69-83 3. CMX001 Cidofovir showed positive results in PML and also its in-vitro activity on Polyoma virus were good enough. Thus further investigations on cidofovir were continued for enhanced BBB penetration, and a lipid conjugate of cidofovir was derived by Chimerix. Inc. which was named as Brincidovir. Also its Phase- II trial showed prevention of Cytomegalo Virus infection. Many clinical trials were completed which shows CMX001 to prevent Cytomegalovirus by Sponsor Chimerix-A North Carolina Based Company. A study was conducted which states that CMX001 suppresses JC virus replication in human fetal brain SVG cell cultures. It also inhibits replication of Polyomavirus. One case report was published of Idiopathic CD4+ Lymphocytopenia patient was survived and responded well to the treatment. It was effective in small doses, thus chances of side-effects seen were also less. CMX001 can also pass BBB, thus it is an effective drug for the treatment of PML.84 4. Mefloquine Mefloquine has been used widely for prophylaxis and treatment of malaria. Mefloquine was found to inhibit JC virus replication in patients given Mefloquine for malaria. This activity showed the ability to inhibit infection with JCV strains. A case report of a 54year old female patient with Sarcoidosis showed decrease in Brain Lesions. It was the first report of successful treatment of PML with mefloquine. 2000 Approved drugs were assessed for Anti JCV activity and various drugs were checked for Anti JCV action and also devoid of cellular toxicities. Only Mefloquine was reported to show high penetration in CNS. Also in vitro studies showed that mefloquine inhibits the viral infection rates of three different JCV isolates, JCV(Mad1), JCV(Mad4), and JCV(M1/SVEcp), and does so in three different cell types, transformed human glial (SVG-A) cells, primary human fetal glial cells, and primary human astrocytes. Mefloquine Inhibits viral replication in cells after viral entry. Although no suitable Animal model is available literature review suggests that mefloquine could be an effective therapy for PML. A ten case reports were assessed from 2010 to 2014 in which mefloquine was used as a treatment along with HAART. Out of them 2 patients responded to the therapy, however among these two patients, one patient of Germany with Idiopathic CD4+ lymphocytopenia and one Patient of Australia with Waldenströmâs macroglobulinaemia, but the treatment was started late namely 2months and 5 months respectively after onset of PML. Because these were all single patients that were treated it is impossible to say with certainty that the improvement was due to Mefloquine. Although these results, along with the in vitro results were promising. However, a larger clinical trial with a total of 37 patients in 2013 was terminated prematurely, because the Data Safety Committee predicted a small probability of showing a significant difference in the outcome of the different groups in this study. Until the termination of the study, no activity of Mefloquine was observed. However, the number of patients was very limited. Also the patients were having various comorbid diseases and thus their survival chances were also varying. These combined facts, makes result to be in suspect, even if the study had not been terminated. Also expert opinions suggested that Mefloquine have toxicities which are long lasting and some are life-long. Thus it was not considered for further study.85,86 5. Cytarabine Cytarabine is a chemotherapeutic agent used mainly as treatment for haematological malignancies such as acute myeloid Leukemia (AML) and Non Hodgkin lymphoma. It affects the duplication of DNA and can therefore be a candidate for PML treatment. Cytarabine can, however, cause severe side effects, especially immune suppression. Eight case reports have been published till date and four among them were HIV infected. Out of these 8 patients, 7 showed response to the treatment with Cytarabine. The patients that did not respond had chronic lymphatic Leukemia. However, a study with 4 HIV infected patients treated with cytosine arabinoside showed no effect of the treatment, all 4 patients died within 71 days after the start of the therapy. Moreover, two larger studies showed no effect of Cytarabine on patients suffering from PML. In a multi-centre trial, 57 HIV patients with PML were randomly assigned to receive one of three treatments: antiretroviral therapy alone, antiretroviral

therapy plus intravenous Cytarabine, or antiretroviral therapy plus intrathecal Cytarabine. At the time of the last analysis, 14 patients in each treatment group had died, and there were no significant differences in survival among the three groups. Thus Cytarabine administered either intravenously or intrathecal does not improve the prognosis of HIV- infected patients with progressive multifocal Leucoencephalopathy who are treated with the antiretroviral agents. 19 Non-Aids patients with PML were treated with IV Cytosine Arabinoside 2mg/kg per day for 5 days. Out of them 7 patients showed improvement within 6 months. Thus cytosine arabinoside showed 36% (7 out of 19) improvement. Also significant bone marrow toxicity was associated with the treatment. Therefore, it is very difficult to draw any solid conclusions from these results. Other clinical trials also did not show significant increase of survival chances while treated with Cytarabine.87,88 6. Topotecan Topotecan is a chemotherapeutic agent primarily used in the treatment of cancer. Topotecan inhibits topoisomerase I and thereby DNA replication. The administration of Topotecan via an implanted ventricular reservoir can overcome the inability of Topotecan to cross the BBB. One non controlled clinical trial with 11 HIV patients where Topotecan was used showed a possible effect of Topotecan on lesion size and survival time. It was seen that Survival time increased and only 3 patients were survived. 89 7. 5HT2 Antagonist Drug -Risperidone One more drug acting on serotonin receptors and was also suggested as a possible treatment of PML is the antipsychotic Risperidone. A case report of non-Hodgkin lymphoma patient responding to Risperidone was also reported.90 8.5HT2 Antagonist Drug-Mirtazapine Mirtazapine is an antidepressant which activates serotonin receptors in the brain and is able to cross the BBB. It has been suggested that JCV uses those serotonin receptors to infect the central nervous system, therefore, mirtazapine can be a suitable drug in the treatment of PML. One case report, a polycythaemia Vera patient, and 4 HIV infected patients case series have been published, all with positive outcome. All 5 patients responded to the therapy. However no clinical trials have been reported for this drug. Apart from all the drugs Mirtazapine was studied for further investigation as Cidofovir, CMX001 were used for the treatment of PML but very less work was conducted on 5HT2 Antagonist drugs and also Mirtazapine shows good results in treatment of PML.91,92 Table:-3.4 Mirtazapine case reports Srno No. of case reports Drug Co-morbidity Positive outcome(yes/no) 1 1 Mirtazapine Polycythaemia Vera Yes 2 4 Mirtazapine HIV Yes 3 1 Mirtazapine Plus Cidofovir Sarcoidosis Yes 4 3 Mirtazapine Plus Mefloquine 2 patients with Multiple sclerosis and 1 with HIV Yes 5 1 Mirtazapine Plus Cytarabine Dermatomyositis Yes Total=10 A case report of 63 year old polycythaemia patient was reported in which Mirtazapine showed efficacy and the patient was neurologically stable with resolution of cerebral lesion. Also Mirtazapine showed efficacy in HIV infected PML patient in one case series. 15mg of Mirtazapine was given weekly to the patient for 6 months in 4 HIV patients. Among them 1 patient showed improvement in MRI and 3 patient showed improvement in Neurological functions. Clinical improvement was seen in patient who received mirtazapine therapy closest to PML symptoms onset period. From these case series, we can conclude that Mirtazapine is safe, well tolerated and offers marked benefits as a treatment or prophylaxis of PML. One more case report of 45 year old man with systemic sarcoidosis treated with combination therapy of cidofovir and Mirtazapine showed significant improvement. Thus mirtazapine shows good results when used in combination therapy for the treatment of PML. A combination treatment of Mirtazapine and Mefloquine on 3 patients also showed positive outcomes. Studies with combination therapy. Several case reports where PML patients have been treated with combination of at least one of the above mentioned drugs has been reported. One patient with PML was treated with cidofovir in combination with chlorpromazine. Chlorpromazine is a drug that may be prescribed for symptoms, like to control vomiting and nausea, to manage psychotic disorders and as a complement in the treatment of tetanus. In vitro experiments show that Chlorpromazine, is able to inhibit viral spread when given in low doses with neutralizing anti-JCV antibodies. Most likely because chlorpromazine is able to inhibit clathrin-dependent endocytosis by inhibiting the disassembly of the clathrin at the plasma membrane as well as inhibiting receptor cycling there. Without the antibodies the same results can be obtained at higher doses. However, there are significant side effects at higher doses. Chlorpromazine

might be able to cross the BBB. The chronic lymphatic Leukemia patient treated with chlorpromazine and cidofovir showed no response to the treatment. Two reports of combination therapy with IL-2 have been published, one is along with cytarabine and another in combination with cidofovir. Response were seen on patients treated with Cytarabine and this patient had underwent autologous bone marrow transplant. Four reports on the combination of cidofovir with cytarabine have been published, all patients responded to the treatment. One patient having chronic lymphatic leukemia, the other three were HIV infected. One report on the combination of cidofovir with mirtazapine has been published, the sarcoidosis patient responded to the treatment. Three reports on the combination of mefloquine with mirtazapine have been published, all the patients responded to the treatment. Two patients were suffering from multiple sclerosis and one was HIV infected. Combination therapy of Cytarabine and mirtazapine has been published in one report, the Dermatomyositis patient responded to the treatment. Two reports on the combination of Cytarabine and INF-Ŭ have been published, both patients responded to the therapy. One patients had Cröhn disease the other one sarcoidosis. One report on the combination of mefloquine, mirtazapine and cytarabine was published, response was not good enough in patient with chronic lymphatic leukemia. Most of reports show a responds of the patient to the different therapies.93,94 Outcome of combination Therapy:- Combination therapy shows good results but according to the expert opinions, orphan designations are given to single drug molecules only, combination drugs does not covers orphan designations. Thus combination drugs although used offline cannot be orphan designated. SEARCH STRATEGY Figure:-3.8 theprocess flow we followed to target a drug regimen for PML is as follows:- Drug Screening and to find possible target mechanisms of PML Data support (Extensive Literature Search And Scientific Evidence) and Data Mining for PML. To assess and evaluate whether the drug development is cost effective or not. Experts Opinion (Research areas, Principle Investigators of clinical trials), Feedback on queries Collection of data of Commercial Benefit and Scientific Interest (Worldwide) Commercial cost will be calculated from Incidence of PML and data cost (Medical cost) of disease treatment in patient Reviewing for Medicine re- imbursement as PML is more prevalant in US and EU. Clinical Development Outlook/ Clinical Trial Design for targeted drug Application for Orphan drug designation Methodology in detail:- 1. Drug screening and to find possible mechanisms Various drugs used in the treatment of PML is assessed and evaluated for its efficacy for the treatment of PML on the basis of case reports and data available by extensive literature search. 2. Data support and Data mining After completing extensive literature search and target screening, number of evidence will be found for that particular approach. The strength of evidence will provide main benefit of approaching drug for PML. This can be done by more literature search, combining and interpreting all available data. 3. Expert opinion For drug repurposing, the expertŝ opinion will be considered as an important factor. Expert opinion will be taken from research scholars, principle investigators of different clinical trials. 4. Commercial benefit and Scientific interest As drug repurposing is carried out for main two purpose, treating diseases with unmet medical and cost effective approach as new drug discovery required lots of money investment. Commercial cost will be calculated from Incidence of that disease and data cost (Medical cost) of disease treatment in patient. Thus how commercial benefit will be found. Additionally country like U.S. gives medical re- imbursement for particular diseases. So, that will provide more benefit to the pharma-companies and to the patients also. Scientific interest will be found from the strength of evidence of work for the particular drug (if you are working on disease driven approach than the evidence of work done on that disease and different mechanism of drug on that disease therapy) 5. Clinical trial design/ clinical trial outlook and Applying for orphan drug designation in EU/US market At the last step to drug repurposing clinical trial should be design with the help of primary and secondary endpoints related to drug, dose and effectiveness. After that clinical trial should be carried out to confirm the effect of the drug in the particular disease. At last the one can apply for orphan designation in EU/US market and get additional benefit. RESULTS To date there is no viable treatment for PML. Only few medications show favorable results in certain case reports. Drugs such as IFN-Ŭ, cidofovir, cytarabine and mefloquine that was evaluated

in clinical trials, showed no significant results. Cidofovir is not convincing against PML, most likely on the grounds that it can't pass the BBB. Then again, an enhanced cidofovir drug, CMX001, shows promising results in vitro on cell lines, it can pass the BBB and showed improvement according to the case report. Mefloquine additionally shows promising results in vitro, and even in vivo case reports look encouraging, however a clinical trial with 37 patients was ended rashly in light of the fact that impact of mefloquine was not measurable. Cytarabine is generally tried for numerous situation reports, a number of the patients reacted to the medication. Also in clinical trials, no huge impact was measurable. Immunomodulating drugs such as IL-2 shows fair results in certain case reports but, it is not tried in clinical trials. INF-Ŭ has been indicated but it does not showed marked improvement. A patient did not show any improvement to the treatment of INF-ɓ thus it was not studied further. Chlorpromazine has only one case report in which the patient did not showed any improvement to the treatment. Serotonin receptors antagonist drugs such as risperdone and mirtazapine show quite good results in case reports. Additionally, mirtazapine shows even more worthy results in the case reports where it is utilized in combination with different medications. But no clinical trial has been reported for these drugs. Many combination therapies have been used offline but none of them have been tried for clinical trial. Hence we cannot further study these combinations without proofed data and evidences. A trial for topotecan was reported and 3 out of 11 patients showed improvement in brain lesion. DISCUSSION PML is demyelinating rare disease of the brain triggered by the JC virus (JCV), it has a serious impact on patients who experience the ill effects of it and even the death rate is high. Patients with very weak immune system are affected by this disease. Patients treated with Natalizumab as a treatment regimen for multiple sclerosis are at highest risk of PML. To date, there is no convincing treatment found to treat PML. Challenges in finding treatment for such disease lie in a scope of reasons. To begin with, there is no animal model as JC virus replication does not occurs in non-humans. Thus preclinical testing cannot be carried out to assess effect of any drug on PML. Another reason is PML is an orphan disease, hence a patient pool with similar background of medical history and disease are impossible to find for conduction of clinical trial. We cannot get large number of patient pool and due to this drug efficacy cannot be proved with less sample size. Also underlying causes of the disease will vary from patient to patient for e.g.:- immune system can be compromised due to multiple reasons such as different drugs like Natalizumab, rituximab, Efalizumab/Alemtuzumab or by disease such as HIV and even due to organ transplantation. The underlying cause and stage differs and due to this strong conclusions cannot be obtained in clinical trials. Research done in context of PML is very limited as it is an orphan disease; very less research has been conducted on JC virus mechanism and replication process. The treatment of PML becomes more complex as the drug targeted should have blood brain barrier crossing property. Cidofovir was effective invitro but as it does not penetrate BBB, it was failed in vivo. A derivative of cidofovir named CMX001 shows good results in case reports as it can cross BBB. Immunomodulating drugs cannot cross BBB and also they cannot be used in the treatment of PML in transplantation patient as rise in immune system due to them may result in rejection of the transplanted organ. Drugs such as Mefloquine, Risperidone and Mirtazapine were able to cross BBB and also Mirtazapine was showing comparatively good outcomes it was investigated further. CONCLUSION From all the drugs reviewed it was assessed that CMX001, Mirtazapine and Risperidone were most encouraging. These drugs can cross Blood Brain Barrier, have no severe side effect and shows positive results in case reports and in in vitro studies. However, none of these drugs have been tested in controlled clinical trials, so further research is needed for these drugs. CMX001 is a patented drug thus taking Mirtazapine as a suitable drug regimen for PML and from all the evidences, clinical trial design for Mirtazapine is designed for further progress and research. A proposed trial design for Mirtazapine is as follows:- Mirtazapine Trials Design Title: - A Randomized Study to Explore the Effect of Mirtazapine in Subjects with initial stage infection of PML. Study Type: - Interventional Study Phase: - Phase-III Condition: - PML Intervention: - Drug: - Mirtazapine and Placebo Dose: - 15mg orally Sample Size: - 36 Rational for Drug, Dose and Sample Size selection:- As mentioned in previous sections of this thesis, Mirtazapine has

been found to be useful in early stage of PML to reduce the JC virus load. This study is designed to evaluate the effect of Mirtazapine compared to Placebo for the early stage cases of PML. The dose selected for this study is based on series of case reports published in reputed journals. The sample size has been considered respect to prevalence of disease (5 in 10,000) and previously conducted clinical trials. Design:- Placebo control. Treatment Duration: - 24 weeks Identification techniques:- MRI and detection of JCV in CSF and decreased levels of CD4+ (normal range 500-1500) and CD8+ (normal range 250-950 cells per mm3) is used as a diagnostic tool to detect PML. Viral load more than 1000 copies/ml are seen. (Normal range of viral load is less than500 copies/ml) Symptoms of PML:- ? Loss of co-ordination. ? Loss of language ability ? Seizures and hemiparesis ? Memory loss ? Vision Problems ? Weakness of the legs and arms. Medications which cause or aggravate PML:- ? Rituximab ? Natalizumab ? Alemtuzumab ? Cyclophosmamide ? Prednisolone ? Mycofenolatemofetil ? Tacrolimus ? Dexamethasone Eligibility Criteria: - Inclusion Criteria: ? Diagnosis of PML confirmed by detection of JCV DNA in CSF. ? Age within 18 to 70 years. ? Patient who has given his/her informed consent, and signed the consent form. ? Non pregnant and non-lactating women. ? Patients willing to undergo MRI and other study procedures. ? Life Expectancy at least 1 year ? Onset of PML symptoms within 6 months prior to study (Infection in Initial stage) Exclusion Criteria: ? Other opportunistic infection of the central nervous system such as toxoplasmosis, multiple sclerosis, neurosyphillis etc. ? Patients with severe malignancies such as brain tumour and Kaposi Sarcoma and diseases such as hepatitis and Sickle cell anaemia. ? A history of drug abuse in the 6 months prior to screening. ? Medical contraindication to MRI (i.e., devices such as a cardiac pacemaker or infusion pump, other metallic implants, metallic foreign objects, body piercings that cannot be removed) ? Woman of child bearing potential not protested by effective contraceptive method of birth control and/or are willing or unable to be tested for Pregnancy. ? Active severe mental illness (e.g., depression, anxiety, psychosis, and schizophrenia). ? Hypersensitivity to mirtazapine, serotonin inhibitors or to any component of these drugs. ? Current treatment with Mirtazapine due to other ailments. ? Patients with Current participation in other clinical trials. Primary outcome measure:- The primary objective of the study was to explore whether mirtazapine can delay or stop progression of PML at initial stages as measured by JC virus load in cerebrospinal fluid (CSF). Secondary outcome measure:- The secondary objective of the study was to explore whether mirtazapine can delay or stop progression of PML at initial stages based on neurological deterioration, magnetic resonance imaging (MRI) measures of brain lesion evolution or the formation of new lesions, and mortality. Primary Endpoints:- ? Change from Baseline to week 8,16 and 24 in JC Virus Load(viral load less than 500 copies/ml) [Time frame :- week 0, 8, 16, 24] Secondary endpoints:- ? Marked improvement in brain lesions from week 0 to week 16 and 24 for the experimental arm v/s placebo arm. ? Change from baseline to week 16 and 24 in the Expanded Disability Status Scale (EDSS) Score and normal range of CD4+ and CD8+. ? Change from baseline to week 16 and 24 in Karnofsky Performance scale. ? Change from Baseline to Week 16 and Week 24 in Participants' pain scores using a Visual Analog Scale (VAS). Rescue treatment strategy:- Patients diagnosed with PML infection at initial stage are recruited in the study. The stage of PML is detected mainly by viral load in cerebrospinal fluid. Normal range of CSF is less than 500 copies/ml. Patient is given mirtazapine 15mg for first three days and then it is given weekly for 6 months. If there is no improvement in viral load or if viral load increases than immediately the patient is given approved therapy like drugs such as IL-7, Imatinib, CMX001 and other treatment regimen to prevent further increase in viral load. Schedule of Assessment Scree ning Treatment Follow up Procedures -14 days Day 1 Day 28 Day 56 Day 84 Day 112 Day 140 Day 168 Day 196 Day 224 -14 to 0 Week 0 Week 4 Week 8 Week 12 Week 16 Wee k 20 Week 24 Wee k 36 Week 48 Day 3days/ week Informed Consent × Screening; Inclusion/Excl usion Criteria × Medical History, Demographics × Randomization × Physical Examination × CD4+ and CD8+ counts × × × Vital Signs × × × × × × × × × × Dose × × × × × × × CSF determination × × × Brain lesion (MRI) × × × Symptomatic assessment × × × × × × × × × Treatment History (Prior medication) × Concomitant medication × × × × × × × Adverse events × × × × × × × × × Visual Analog Pain Scale (VAS) × ×

× EDSS Score × × × Karnofsky Performance scale × × × Vital signs, concomitant medications, adverse effects, pain analogue scale, will be performed on before or after dosing. Randomization is done by sealed envelope method. Dose of Mirtazapine is 15mg for first three days and then it is given weekly. Chapter 2 [Pick the date] Institute of Pharmacy, Nirma University Page 2 Institute of Pharmacy, Nirma University Page 3 Institute of Pharmacy, Nirma University Page 4 Institute of Pharmacy, Nirma University Page 5 Institute of Pharmacy, Nirma University Page 6 Institute of Pharmacy, Nirma University Page 7 Institute of Pharmacy, Nirma University Page 8 Institute of Pharmacy, Nirma University Page 9 Institute of Pharmacy, Nirma University Page 10 Institute of Pharmacy, Nirma University Page 11 Institute of Pharmacy, Nirma University Page 12 Institute of Pharmacy, Nirma University Page 13 Institute of Pharmacy, Nirma University Page 14 Institute of Pharmacy, Nirma University Page 15 Institute of Pharmacy, Nirma University Page 17 Institute of Pharmacy, Nirma University Page 19 Institute of Pharmacy, Nirma University Page 20 Institute of Pharmacy, Nirma University Page 21 Institute of Pharmacy, Nirma University Page 22 Institute of Pharmacy, Nirma University Page 23 Institute of Pharmacy, Nirma University Page 24 Institute of Pharmacy, Nirma University Page 26 Institute of Pharmacy, Nirma University Page 27 Institute of Pharmacy, Nirma University Page 28 Institute of Pharmacy, Nirma University Page 29 Institute of Pharmacy, Nirma University Page 30 Institute of Pharmacy, Nirma University Page 31 Institute of Pharmacy, Nirma University Page 32 Institute of Pharmacy, Nirma University Page 33 Institute of Pharmacy, Nirma University Page 34 Institute of Pharmacy, Nirma University Page 35 Institute of Pharmacy, Nirma University Page 36 Institute of Pharmacy, Nirma University Page 37 Institute of Pharmacy, Nirma University Page 38 Institute of Pharmacy, Nirma University Page 39 Institute of Pharmacy, Nirma University Page 40 Institute of Pharmacy, Nirma University Page 41 Institute of Pharmacy, Nirma University Page 42 Institute of Pharmacy, Nirma University Page 43

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paper text:

58**Head and Neck Cancer** Cancer **of the** region from **the** neck **and**

above is referred to as Head and Neck Cancer (HNC) or Oral

23**Cancer. Most head and neck cancers begin in the cells that line the mucosal surfaces in the head and neck area, e.g.,**

10**mouth, nose, and throat. Normal mucosal cells look like scales (squamous) under the microscope, so head and neck cancers are often referred to as squamous cell carcinomas. Some** head and neck **cancers begin in other types of cells.**

56**For example, cancers that begin in glandular cells**

10**are called adenocarcinomas. Cancers of the** oral cancer **are** further identified **by the area in which they begin:-**

Å

28**Oral cavity • Salivary glands • Paranasal sinuses** and **nasal cavity • Lymph nodes in the upper part of the neck.**

ÅPharynx ÅNasopharynx ÅOropharynx ÅHypopharynx 1,2 Figure 2.1 Head and Neck Cancer Regions Epidemiology

34**Overall, head and neck cancer accounts for more than 550,000 cases annually worldwide.**

2**Males are affected significantly more than females with a ratio ranging from 2:1 to 4:1. The incidence rate in males exceeds 20 per 100,000 in regions of France, Hong Kong, the Indian subcontinent, central and Eastern Europe, Spain, Italy, Brazil and among African Americans in the Unites States. Mouth and tongue cancers are more common in the Indian subcontinent, nasopharyngeal cancer is more common in Hong Kong, and pharyngeal and/or laryngeal cancers are more common in other populations.** 3 **In the United States,**

head and neck cancer accounts for 3 percent of malignancies, with an estimated 55,000 Americans developing head and neck cancer annually and 12,000 dying from the disease. The incidence of laryngeal cancer, but not oral cavity and pharyngeal cancer, is approximately 50 percent higher in African-American men. The mortality associate with both laryngeal and oropharyngeal cancer is significantly higher in African American men, which may reflect the lower prevalence of HPV positivity. 3 Etiology/Pathophysiology

3**Head and neck cancer arises from a series of molecular alterations progressive from dysplasia to carcinoma in situ and finally invasive carcinoma.**

3**There are genetic alterations in pre-cancerous cells that contribute to transformation. The accumulation of these alterations facilitates tumor development. Additionally, the tumor microenvironment enables tumor progression. The cooperative effect of molecular alterations in the tumor cells and compensatory microenvironment changes enable tumors to invade and metastasize.**

9**Genetic and epigenetic alterations may lead to protein changes including**

decreased or increased expression. The accumulation of these alterations in oncogenes, proto-oncogenes **and tumor suppressors can lead to the** formation **of** a malignancy. **Critically altered pathways in**

62**Head and Neck Squamous Cell Carcinoma**

include p53,

9**epidermal growth factor receptor, signal transducer and activator of transcription 3 and vascular endothelial growth factor receptor, among other important molecules that may serve as therapeutic targets.**

4 Risk factors/Causes ÅTobacco (chewing and snuffing) ÅAlcohol Å

10**Sun exposure (lip); possibly human papillomavirus (HPV) infection**

ÅDiagnostic x-rays /

38**radiation therapy • Industrial** exposures, **such as wood or nickel dust inhalation**ÅEpstein-Barr virus Å**Exposure to**

airborne particles of asbestos 5 Signs & Symptoms Å

24**Lump or sore that does not heal • Sore throat that does not go away • Difficulty swallowing • Change or hoarseness in the voice**

ÅOral cavity:

43**A white or red patch on the gums, tongue, or lining**

30**of the mouth;** a **swelling of the jaw that causes dentures to fit poorly or become uncomfortable; and**

unusual bleeding or pain in the mouth. ÅNasal cavity and sinuses:

16**Sinuses that are blocked and do not clear, chronic sinus infections that do**

not respond to treatment with antibiotics, bleeding through the nose, frequent headaches, swelling or other trouble with the eyes, pain in the upper teeth, or problems with dentures.

Å

27Salivary glands. Swelling under the chin or around the jawbone; numbness or paralysis of the muscles in the face; or pain

50that does not go away in the face, chin, or neck.

5 Diagnosis/Physical Examination/Tests ÅPhysical examination may include visual inspection of the

21oral and nasal cavities, neck, throat, and tongue using a small mirror and/or lights. The doctor may also feel for lumps on the neck, lips, gums, and cheeks.

ÅLaboratory tests

17examine samples of blood, urine, or other substances from the body. • X-rays create images of areas inside the head and neck on film.

Å

17Endoscopy is the use of a thin, lighted tube called an endoscope to examine areas inside the body. The

type of endoscope the doctor uses depends on the area being examined.

36For example, a laryngoscope is inserted through the mouth to view the larynx;

an esophagoscope is inserted through the mouth to examine the esophagus; and a nasopharyngoscope is inserted through the nose so the doctor can see the nasal cavity and nasopharynx. Å

13CT (or CAT) scan is a series of detailed pictures of areas inside the head and neck created by a computer linked to an x-ray machine. • Magnetic

> **resonance imaging (or MRI) uses a powerful magnet linked to a computer to create detailed pictures of areas inside the head and neck.**

Å

> 49**PET scan** uses sugar that **is modified in a specific way so**

it is absorbed by cancer calls and appears as dark areas on the scan.

> 20**Biopsy is the removal of tissue. A pathologist studies the tissue**

> 29**under a microscope to make a diagnosis. A biopsy is the only sure way to tell whether**

> 15**a person has cancer. • If the diagnosis is cancer, the doctor will want to learn the stage (or extent) of disease. Staging is a careful attempt to find out whether the cancer has spread and, if so, to** which **parts of the body.**

Staging may involve an examination under anesthesia (in the operating room),

> 20**x-rays and other imaging procedures, and** laboratory **tests. Knowing the stage of the disease helps the doctor plan treatment.**

TNM staging: Å

> 4**T describes the size of the tumour. • N describes whether the cancer has spread to the lymph nodes and which nodes are involved. For example, N0** means that **no lymph nodes** are **affected, while N1 means there are cancer cells in the lymph nodes. • M describes if the cancer has spread to another part of the body. For example, M0 means the cancer has not** metastasized **to other parts of the body.**

Biomarkers: ÅEGF, EGFR, IL-8, tPAI-1, AFP, MMP-2, MMP-3, IFN- - -10, RANTES, MIP- IL-7, IL-17, IL-CAM, and CA-125 -2R, G-CSF, mesothelin, IGFBP-1, E-selectin, cytokeratin (CK)19, V- Treatment & Management Treatment includes the following ï Chemotherapy ï Radiation therapy ï Surgery ï Combination Chemo-Radio therapy Chemotherapy: ÅAlkylating agents: Cisplatin ÅAntimetabolites: Methotrexate ÅAntitumor Antibiotics: Doxorubicin, Bleomycin ÅAlkaloids: Vincristine, Vinblastine ÅTaxanes:

Paclitaxel Radiation therapy: Å

> 5**Radiotherapy can be given in two ways: – From outside the body as external beam radiotherapy. A beam of x-rays or electrons**

is directed at the cancer

> 5**from a large machine called a linear accelerator. This is the most common way of giving radiotherapy to the head and neck area. – By** putting a **radioactive** source **into the tumour and leaving it there for a few days. This is known as internal radiotherapy, interstitial radiotherapy or brachytherapy.**

Surgery: ÅThe surgeon

> 7**may remove the cancer and some of the healthy tissue around it. • Lymph nodes in the neck may also be removed (lymph node dissection), if the doctor suspects that the cancer has spread.**

ÅSurgery may be followed by radiation treatment. Chemoradiation therapy: ÅChemoradiation is often the main treatment for advanced head and neck cancers. It may be used as follows:- ÅTo treat cancers that cannot be removed with an operation. ÅTo treat cancersin hard to reach areas such as the nasopharynx or throat when surgery could cause unacceptable changes to speech or swallowing. Patient Management Å

> 32**Head and neck surgery often changes the patient's ability to chew, swallow, or talk.**

The patient may look different

> 6**after surgery,** and **the face and neck may be swollen.**

ÅAfter a laryngectomy (surgery to remove the larynx), parts of the neck and throat may feel numb because nerves have been cut. Ålf lymph nodes in the neck were removed, the shoulder and neck may be weak and stiff. Å

> 7**Patients who receive radiation to the head and neck may experience redness, irritation, and sores in the mouth; a dry mouth or thickened saliva; difficulty in swallowing; changes in taste; or nausea.**

ÅOther problems that may occur during treatment are loss of taste, which may decrease appetite and affect nutrition, and earaches (caused by hardening of the ear wax). Å

> 6**Patients may also notice** some **swelling or drooping of the skin under the chin and changes in the texture of the skin.**ÅThe jaw **may** feel **stiff and** patients **may** not be able **to open their mouth as wide as before treatment.**

Patients may have

> 6**side effects** such **as lower resistance to infection, sores in the mouth and on the lips, loss of appetite, nausea, vomiting,** diarrhoea, **and hair loss.**

ÅThey may also feel unusually tired and experience skin rash and itching, joint pain, loss of balance, and swelling of the feet or lower legs. Recommendations: ÅStop smoking ÅCut down on alcohol ÅMaintain good oral hygiene ÅEat healthily ÅRegular dental check-ups and treatment ÅPatient counseling 5 Supportive care The

> 48**SPIKES protocol (Setting, Perception, Invitation, Knowledge, Empathy** and **Strategy) can be**

a helpful framework for head and neck oncology. This includes taking adequate time to talk to the patient, asking their understanding of the disease and inviting them to express how much they want to know, how they want to be told, and who they want to have with them. Language used should be understandable, with silences to allow news to be taken in. Clinicians should show empathy to the range of emotions presented by the patient and the family, and patient should leave the consultation with a plan of care.6

> 40**Quality of Life (QOL) The World Health Organization defines QOL as**

ñan individualôs perception of their position in life, in the context of the culture and values systems in their life, and in relation to their goals, expectations, standards, and concernsò

> 22**QOL measures seek to obtain a comprehensive, multi-dimensional picture of the patient's**

ñtotal health related experience.ò

> 1**Quality of Life (QOL) has become an increasingly important outcome measure for patient's undergoing treatment for a wide array of illnesses.**

> 14**Length of survival alone is an unsatisfactory measure of the success of treatment; the quality of survival needs to be evaluated.**

> 1**QOL is a global construct that reflects a patient's general sense of well-being. It is by definition multi-dimensional and reflective of the patient's point of view. Health related issues are among the many factors that may influence QOL. Since Head and Neck Cancer (HNC) affects structures that are critical for normal functions such as speech and**

> 39**swallowing, and treatment may lead to deformities that adversely impact psychosocial functioning,**

there is particular interest in assessing QOL in this cohort of patients. Whether routine use of QOL measures in the clinical setting is beneficial to patients or not has yet to be determined. Further studies are warranted. Significance of QOL in HNC: Å

> 63**QOL data can provide information that**

guides health care related decision making on several levels. ÅFirst it

> 14**can help shape public policy and health care decisions made by governmental and private institutions.**

It can also

> 14**guide the research agenda of pharmaceutical companies and cooperative groups.**

Å

> 22**Most importantly, QOL measurement can provide information to guide clinical decision making.**

ÅQOL studies should inform the practitioner about the impact of specific treatments on outcomes. ÅThis information can then be shared with patients and used to help make decisions regarding treatment options. By providing concrete information about outcomes, QOL studies can Åfacilitate communication between a

physician and their patient Åidentify problems that have a significant impact on QOL Åguide the physician to screen for problems that impact QOL ÅHelp physicians prioritize the treatment of problems that develop during treatment. Aim and Objectives The routine use of quality of life questionnaires among cancer patients enables health practitioners to discover in which areas and to what extent patients find their lives affected by the treatment they receive and its consequences. This allows health practitioners to provide information and treatments which are better adapted to patient needs. This study aimed to investigate the health-related QOL characteristics in Oral Cancer patients reconstructed with PMMF with the following objectives: ? To evaluate the compatibility of PMMF at both donor and recipient sites. ?

19**To assess the quality of Life of** oral cancer **patients** after reconstruction **with**

PMMF. ? To investigate the risk factors and to find out correlationsbetween all 12 domains,parts affected and risk factors. 3. Review of Literature 3.1Background of

51**Quality of Life Quality of Life** implicates on **the** patientõs state **of**

well-being. Questionnaires raise the important issue of what is ñquality of lifeò? Something known that cannot be told, whilst to the researcher it is a difficult measurement problem, and to the clinician it is just one of many other equally relevant inputs into a clinical judgment.

41**Health-Related Quality of Life (HRQOL) is an important outcome parameter**

following

25**treatment for head and neck cancer. The** value **of**

this concept has become established during the last decade. The impact of

46**head and neck cancer and** its **treatment can have** such **a** profound detrimental effect **on**

function and well-being that

47**it is** essential **that the** patientõs **perspective is taken into account.** Two national bodies, **the**

25**British Association of Head and Neck Oncologists** and the **British Association of Otorhinolaryngologists- Head Neck Surgeons,**

both recommend that HRQOL should be longitudinally recorded. Questionnaires give a structured insight into the patientôs point of view. They facilitate multidisciplinary team working with the recognition of poor outcome groups, better information for the patient and their caregivers, and the opportunity to identify problem areas and target support/intervention. The choice of the HRQOL questionnaire depends on the purpose of the study, its design and the available resources. Certain questionnaires may be more applicable in routine practice and others in a research setting.7 3.2 Questionnaires It is time consuming and a logistical challenge to ensure patients self-complete questionnaires before treatment and at regular intervals subsequently. Very few units are currently collecting HRQOL information and one of the problems has been the selection of the most appropriate questionnaire. There will never be a perfect head and neck questionnaire and there is a choice between about 14 validated measures. The most commonly used are the EORTC, FACT and UW-QOL. However HRQOL data collectionremains a low priority in many units. One reason for this is that some questionnaires are too long or complicated for

55**members of the head and neck team,** including **the**

patient, and seem more suited to research. One questionnaire that has emerged as a simple yet clinically relevant measure suitable for routine clinical practice

18**is the University of Washington questionnaire (UW-QOL).**

8 3.3 The University of Washington Questionnaire

8**In the original description, Hassan and Weymuller stated that**

Ătheadvantages of the UW-QOL head and neck questionnaire are that 1) it is brief and self-administered, 2) it is multi-factorial, allowing sufficient detail to identify subtle change, 3) it provides questions specific to head and neck cancer, and 4) it allows no input from the health provider, thus reflecting the QOL as indicated by the patient.9 The current version 4 of the UW-QOL questionnaire consists of 12 single question domains, these having between 3 and 6 response options that are scaled evenly from 0 (worst) to 100 (best) according to the hierarchy of response. The domains are pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood and anxiety. Another question asks patients to choose up to three of these domains that have been the most important to them. There are also three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. In regard to their overall QOL patients are asked to consider not only physical & mental health, but also many other factors, such as family, friends, spirituality or personal leisure activities that were important to their enjoyment of life. The whole questionnaire focuses on current patient health and quality of life within the past 7 days.10 3.4 Scoring of UW-QOL domains The UW-QOL has domains based upon discrete ordinal responses. Scoring is scaled to so that a score of 0 represents the worst possible response, and a score of 100 represents thebest possible response. Scoring is scaled in equal stages from 0 to 100 to reflect the number of possible responses. Thus the pain domain has 5 possible responses which are scored as 0, 25, 50, 75 & 100. 3.5 Global Questions The UW-QOL has domains and general questions based upon discrete ordinal responses. The UW-QOL asks three global questions, one about how patients feel relative to before they developed their cancer, one about their health-related QOL and one about their overall QOL. These are now also scaled from 0 to 100 to enable ease of

presentation of all key results using the same 0 to 100 scale. The general question asking about overall QOL has 6 possible responses which are scored as 0, 20, 40, 60, 80 & 100.7 3.6 Important question This asks about which three domain issues were the most important during the past 7 days. Patients are asked to choose up to 3 domains,11 Chang et al conducted a study with the aim of translating the UW-QOL questionnaire version 4 into the Korean language and carrying out an initial validation study. 56 patients completed Korean versions of UW-QOL, the Beck Depression Inventory and the World Health Organization Quality of Life-BREF and various expected correlations were confirmed first between the two UW-QOL subscales (Spearman 0.54 $p < 0.001$) and then of these subscales with the other concurrent measures. Lower (worse) UW-QOL scores were seen for later stage patients in all the domains.12 Jornet et al conducted a project to evaluate the quality of life in patients undergoing treatment for head and neck cancer in the Murcia region (Spain). The Quality of Life (QOL) of 109 patients suffering head and neck cancer was assessed using Spanish translations of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 (EORTC QLQ-C30) and Head and Neck Cancer Module(QLQ-H&N35). The questionnaires' scales and single items were compared according to age, sex, tumour location, stage of cancer and treatment type. With regard to the stage of cancer, early stages obtained better scores than advanced ones.

19**Patients who underwent surgical treatment combined with adjuvant radiotherapy and chemotherapy generally showed** lower **scores.**

13 Laraway et al conducted a review to systematically search published papers that report UW- QOL questionnaire's use and identify common themes.

1**A total of** 66 papers **were included in the study,**

out of which 21 were on functional outcome, 25 on predictors of HR-QOL, 19 on development or validation of the questionnaire, and one clinical trial. The questionnaire was first used in the USA and was written in English, but several translations have since been done which show its cross-cultural application. Translations include simplified Chinese, Hindi and Marathi, Brazilian Portuguese, as well as Italian, German, Norwegian, Malay, Greek, Japanese, and Dutch. 3.7 Reconstruction Methods After removal of tumour cells, the functional and aesthetic outcomes are negatively affected. Surgical removal of the primary lesions and excisions of the lymph nodes forms the mainstay of treatment in majority of the cases. The aim of reconstructive surgery after surgical resection in oral cancer malignancies is to restore structure and function as soon as possible with minimum trauma to the patient. Thus to overcome the defects and to improve aesthetic appearance, reconstruction methods are used

52**to ensure** the **good quality of life** after **the** cure **of**

cancer. Various types of reconstruction methods are used which are listed as follows:- 1. Facsiocutaneous free flaps ? Radial forearm ? Lateral arm ? Lateral thigh 2. Muscle and Musculocutaneous free flaps ? Rectus abdominis ? Lattisimus dorsi 3. Composite free flaps ? Radial forearm ? Fibula ? Scapular/Parascapular ? Ilium As malignant tumour are more prevalent in India, Incidence being one third of all new cancer patients and also most of these patients present late in the course of the disease, tumour resection becomes mandatory for them to remove further invasion of tumour cells.

11**Pectoralis Major Myocutaneous Flap is** widely used **as it is**

quick and easy to prepare, reliable and sufficiently close to most oral cancer sites. Its rich blood supply makes the flap extremely safe. Ariyan and krizek were the first to report the use of PMMFin Head and Neck reconstruction. Since then this flap has earned the synonym ñthe workhorse for head and neck reconstructive surgeryòAdvantages

12**of Pectoralis major Myocutaneous** pedicle **flap**

(PMMF) is as follows:- ? ? ?

11**This flap offers one-stage reconstruction. The patient's position need not be changed** intraoperative. **This flap provides a large cutaneous island that can be used for defects involving 2 epithelial surfaces. ? The muscular part covers neck structures protecting the carotid artery, especially in patients who have undergone radiation therapy.**

Now a days Tissue engineering and Microvascular techniques are used as recent advances to overcome bone defects but PMMF are used because of its versatility and cost effectiveness. The

12**PMMF is a flap for huge defects in head and neck reconstructive surgery, in particular when a bulky flap is needed in order to cover the carotid artery.**

Thus it can be concluded that PMMF is the most versatile flap

64**used for head and neck reconstruction.**

14-16 Methodology 4.1Study design Prospective,Single-Centric study involving Oral Cancer patients. 4.1.1 Site of Study Shrey Hospitals Pvt Ltd, Navrangpura, Ahmedabad. 4.2 Study Population Sample Size: - 65 There were 192 consecutive patients between 2011 and 2014 who were treated

59**for head and neck cancer,** amongst them 65 **patients** were having **oral**

cancer and treated with mandibular resections. HRQOL was assessed by

45**University of Washington Quality of Life (UW-QOL) questionnaire version**

four after 3-12 months postoperatively. 4.2.1 Inclusion Criteria ? Adults from age 19 years to 80 years. ?

Patients diagnosed and treated from Oral Cancer. ? Patients of whom surgery has been completed. ? Patients on Chemotherapy and follow-up. 4.2.2 Exclusion Criteria: ? Age below 19 years and above 80 years. ? Adults having any other cancer except that of Oral Cancer. ? Severe co morbid diseases and No healthy volunteers. 4.3 Study Methodology: A prospective, single centric study was designed in which the patients of Oral Cancer after treatment and who were disease free after 6 months of the treatment were recruited and UW- QOL was filled which includes parameters

> 26**such as Pain, Appearance, Activity, Recreation, Swallowing, Chewing, Speech, Shoulder, Taste, Saliva, Mood and Anxiety** were assessed during **the** past seven days **of** operation. On **the** basis **of**

these parameters

> 60**quality of Life of oral cancer patients**

was evaluated. Also patientôs compatibility with reconstruction with Pectoralis Major Myocutaneous Flap was assessed.

> 35**4.4 Ethical Consideration Study protocol was reviewed and approved by the Institute of**

Pharmacy, Nirma University. IEC/NU/15/2/10th April 2015. 4.5 Study Evaluation Criteria ?

> 18**Pain ? Appearance ? Activity ? Recreation ? Swallowing ? Speech ? Shoulder ? Taste ? Saliva ? Mood**

? Habits ? Education ? Socioeconomic status ? Occupation ? Anxiety ? Age ? Gender ? Habits: chewing tobacco or smoking, alcohol ? Education ? Occupation ? Comorbidities ? Compatibility with pectoralis major Myocutaneous flap 4.6 Statistical Analysis Data were recorded, and then

> 33**analysed with the help of the Statistical Package for the Social Sciences (SPSS version**

19). Univariate analysis of variance was carried out and

> 44**P-value less than 0.** 005 **were** accepted **as significant.** Quantitative **results** were expressed as **mean±**

SD. RESULTS Sixty-five patients with oral cancer were included in this analysis. All patients completed the

questionnaire during their visit to the hospital for follow-up. Of the 65 patients who completed questionnaires,

12**there were** 55 **men and 10 women with a** median **age of** 50.5 **(range**

30ï 60) Gender Distribution Male Female 15% 85% Figure 5.1: Gender Distribution of oral Cancer Patients Age Distribution of Patients 25 No.of Patients 20 15 10 No.of patients 5 0 21-30 31-40 41-50 51-60 61-70 Age Figure 5.2: Age distribution of oral Cancer Patients Table:5.1 depicts that Buccal mucosa (N=42, 64.61%) and tongue (N=12, 18.46%) were the most common sites (Followed by alveolus (N=7, 10.76%) and Retro molar trigon (N=4, 6.15%) Forty-nine patients of 65(75.38%) were classified as T1ï T2, while 16 (24.61%) were classified as T3ï T4. The postoperative

12**follow-up period ranged from** 3 **months to** 2 **years,** and the **mean**

follow-up point was 2.5 years. 46 patients were between 1 and 3 years after treatment and the remaining 19 patients had been treated before 3 months. It was observed that buccal mucosa cancer is more prevalent among other cancers in Indian ethnicity. Table:-5.1 patientŝ proforma Variables N % Age <50 years 36 55.38 Ó50 years 29 44.61 Gender Male 55 84.61 Female 10 15.38 Primary Tumor sites Buccal Mucosa 42 64.61 Tongue 7 10.76 Alveolus 12 18.46 Retro molar Trigon 4 6.15 Treatment method Post-Operative Radiation 46 70.76 Post-operative Radiation and Chemotherapy 19 29.23 Tumor Classification T1N0 13 20 T1N1 1 1.53 T2N0 25 38.46 T2N1 3 4.61 T2N2 7 10.76 T3N0 2 3.07 T3N2 1 1.53 T4N0 8 12.30 T4N1 1 1.53 T4N2 4 6.15 Tumour stage

57**of patients** 25 **No.of patients** 20 15 10 **No.of Patients**

5 0 Tumour stages Figure 5.3 Classification of Tumor Stages

53**of oral Cancer Patients Quality of life** UW-QOL: **The**

scores for 12 disease-specific domains and the importance of each domain are shown in table 5.2The best-scoring domain was shoulder and recreation, with the main score of 79.53 and 73.84 respectively. The worst score of the domains are chewing, swallowing and speech, with the main score of 46.15, 48.69, and 53.23 respectively. Amongst selection of the three domains over the past 7 days chewing was considered as most important aspect followed by speech and swallowing. Domains such as recreation, shoulder and mood were considered least important to the patients. Table:-5.2 Domains of UWQOL (v4) questionnaire UWQOL(v4) Mean SD Median Rank Domains order Pain 68.84 28.30 75 10 Appearance 63 19.78 75 7 Activity 55.38 21.87 50 4 Recreation 73.84 22.72 75 11 Swallowing 48.69 22.50 30 2 Chewing 46.15 22.19 50 1 Speech 53.23 27.50 70 3 Shoulder 79.53 22.46 70 12 Taste 56.61 29.22 70 5 Saliva 58.30 34.39 70 6 Mood 64.30 29.08 75 8 Anxiety 64.53 25.07 70 9 About sixty percent patients had low education level. Twenty-two (33.84%) patients did not complete education above 12th standard. Forty-three patients (66.15%) were having education below 12th standard. Consumption of pan, guthka, beedi, tobacco and smoking were highly seen among male patients. Quality of life was negatively affected in higher tumor stages.Some patients were unable to read and write and they need help to complete the questionnaire.

Table:-5.3 Demographic Details Variables N % Employment status Employed 34 52.30 Homemaker 10 15.38 Medical leave 5 7.69 Retired 11 16.92 Chapter 2 [Pick the date] Unemployed 5 7.69 Educational status Above 12th 22 33.84 Below 12th 43 66.16 Addiction Smoking 2 3.07 Tobacco 49 75.38 No addiction 14 21.53 Marital status Married 56 86.15 Unmarried 2 3.07 Widow/widower 7 10.76 Addictions Smoking tobacco No addictions 3% 22% 75% Addiction to the patients. Retromolar Trigone 6% (%)calculation Figure: 5 Percentage of Part Aff Alveolus 18% Tongue 11% Institute of Pharmacy, Nirma University Page 24 Figure 5.5: Parts affected of Oral cavity Positive co-relation with age and risk factor was found and majority of the patients were found to have addiction of Tobacco consumption and smoking. Correlation with age and risk factor 14 12 No. of Patient's 10 8 6 4 2 0 21-30 31-40 41-50 51-60 61-70 Age No. of Patients with Tobacco/Gutkha Consumption No. of Smokers Figure: - 5.6 Correlation with age and risk factor It was found that the age group of 41-61 has the highest rates of Tobacco/Guthka consumption and alcohol addiction. Table:-5.4 Quality of Life Score Distribution Avg. QOL Score Range No. of Patients 0-10 11-20 21-30 31-40 3 41-50 10 51-60 13 61-70 17 71-80 3 81-90 91-100 2 Average Quality of Life Score Range 18 16 No.of Patient's 14 12 10 8 6 4 No.of patient's 2 0 Avg Quality of Life Figure 5.7: Average QOL Score range A majority of the patients (30) have their Avg. QOL Scores in the near median range of 51-70, and a large number of these patients have scores below the same range which represents their reduced QOL. Only 6 patients had their QOL Scores above 70. Table:-5.5Functionality Score Distribution: Avg. Functionality Score Range No. of Patients 0-10 0 11-20 2 21-30 2 31-40 6 41-50 9 51-60 10 61-70 20 71-80 13 81-90 4 91-100 3 Average Functionality Score Range 20 No.of Patient's 15 10 5 No.of Patient's 0 Avg Functionality score range Figure: 5.8 Functionality Score based Distribution of Patients A majority of the patients (N=20) have median functionality scores (61-70) followed by 10 patients in the range of 51-60. Nineteen patients have scores below 50 and 20 patients have scores above 70. Table:-5.6Distribution according to Part Affected Part Affected Avg. QOL Score Compared to a Month before Diagnosis Avg. Functionality Score Avg. QOL Score Buccal Mucosa 87.5 64.46 59.16 Tongue 90.33 58.40 56.87 Alveolus 70.53 54.66 51.42 Retro molar Trigon 90.87 63.42 57.42 This table shows the mean scores of patients according to the part affected. It can be seen that the quality of life score compared to one month before diagnosis is good in comparison of Avg. functionality score and average QOL scores. Table:-5.7 Addiction and Quality of Life Score Risk Habits / Addiction Avg. QOL Score Compared to a Month before Diagnosis Avg. Functionality Score Avg. QOL Score Tobacco/Guthka (N=49) 78.57 61.08 41.63 Smoking (N=2) 100 80.62 60 None (N=14) 80 64 60 This table shows the mean scores of patients with risk habits/addictions and compares them with those of patients with no such habits/addictions. Quality of Life of Tobacco consumers is very low compared to no addiction group. DISCUSSION

61**Health related quality of life** is **an** integrated process for **the**

overall treatment of oral cancer patients. The impact of cancer and its later consequences affects quality of patients life and their families as well. Mandibular resections have their own drawbacks such as it causes unevenness, facial misshape and loss of teeth due to which chewing is compromised. Mandible is involved in crucial activities such as protection of airway passage, support to the tongue and lower dentition. Also it is involved in functions such as speech, mastication and deglutition. Reconstruction of mandibular defects after tumor resection is one of the most challenging problems faced by the plastic surgeons. Also donor-recipient compatibility is very important for the entire reconstruction method. 17 The Myocutaneous flap as a source of vascularized bone in reconstructive surgery is in wide use As it ensures more durable blood supply, also defect at the donor site can be primarily closed and provides tissue bulk to cover large defects. HRQOL has nowadays become a constant provoking question in the assessment of any therapy in oncology. It is time consuming and a logistical challenge to ensure patients self-complete questionnaires before treatment and

at regular intervals subsequently, thus a reliable method should be adopted for obtaining complete details of the patientŝ treatment with ease. In the present study, we have used

> 37**University of Washington Head and Neck Quality of Life questionnaire (UW-QOL)**

version four.

> 8**In the original description, Hassan and Weymuller** et al **stated** the **advantages of the** UW-QOL **head and neck questionnaire are that 1) It is brief and self-administered, 2) It is** multi-factorial, **allowing sufficient detail to identify subtle change, 3) It provides questions specific to head and neck cancer, and 4) It allows no input from the health provider,**

Also UWQOL is widely used questionnaire because it is short and easy for patients to complete themselves, thus making it perfect in a hectic outpatient setup. The current version 4 of the

> 54**UW-QOL questionnaire consists of 12 single** question domains, these **having**

different response options that

> 18**are scaled** evenly **from 0 (worst) to 100 (best) according to the hierarchy of**

response17.we carried out this

> 31**study to determine the** postoperative HRQOL **of** these **patients and the**

possible relationship of reconstruction surgery. The oral specific questionnaire

> 31**was able to** better demonstrate **the** changes **in quality of life**

due to surgery. We can see that the highest score of UW-QOL subscale in present study was in recreation and shoulder domain. The average score was 73.84±22.72 and 79.53±22.46 respectively, patients scored high in pain (68.84±28.30) and appearance (63±19.78) domains, this indicates that mandible reconstruction with Myocutaneous flap have little effect on pain domain. A noteworthy outcome was the relatively low scores of UW-QOL subscales in this study were in speech and swallowing domains. The average scores were 53.23±27.50 and 48.69±22.50, which indicated that mandible reconstruction with Myocutaneous flap have bad effect on speech and swallowing domains. At the same time we found that patients satisfied with the appearance domains. This may be due to the Pectoralis Major Myocutaneous flap (PMMF) as it provides

comparatively satisfactory aesthetic as well as functional reconstruction of mandible defects and thereby obtaining a better aesthetic contour. Though, a significant result was that the lowest score of UWQOL was in chewing (46.15±22.19) domain. This is may be due to mandible defects caused some teeth lost, thus resulting in disorientation of chewing function. Patients believe that surgery has altered their oral functions to a larger extend. In present study, questionnaires do not contain a section on the effect of the Myocutaneous flap donor site on HRQOL and function. But majority of patients reported no serious or any complications in wound healing. A bit strain in shoulder was observed till the wound healing fully completed, after that no complaints were reported for donor site complications. Also as the donor site is covered under clothes it is well acceptable by the patients. The immediate postoperative donor site morbidity is generally considered to be low and is reported to be in a range between 15% and 55. In our study, 21.42 % of the patients specifically males reported problem of hairs at the defect site ashirsute chest skin is placed intraorally. Some studies have mentioned that apart from only surgery the adjuvant radiotherapy and chemotherapy resulted in reduced weight, altered salivary and physical functions. Also functions such as swallowing and chewing were not as same as before and problems of coughing, and dry mouth increased.46/65 patients in our study (70.76%) were given radiotherapy and 19 patients (29.23%) were given both Radiation and Chemotherapy. Among them 38 patients (58.46%) complained about loss of appetite, dry mouth and weight loss after chemotherapy/radiotherapy or both.There were several limitations of this study. First, the

42**sample size was** limited **and may not have** had **sufficient power to find**

more valid and proofed data. Secondly, we collected data after patientÕs treatment during their follow- up, entire pre and post-operative period was not precisely evaluated and so could not fully assess its impact on patient HRQOL over the entire treatment period.18 CONCLUSION ? After mandible reconstruction with Myocutaneous flap significantly influence

19**on the** oral **cancer patient's quality of life,**

especially in patientÕs oral functions. ? Oral Cancer treatment, HRQOL should be accepted as an important outcome parameter, along with the conventional medical conclusions. Clinically, HRQOL should be used as part of oral cancer treatment. The socio-cultural data showed a rather low education level, low economic condition and low standard of living for most of the patients.17 Chapter 2 [Pick the date] Institute of Pharmacy, Nirma University Page 2 Institute of Pharmacy, Nirma University Page 3 Institute of Pharmacy, Nirma University Page 4 Institute of Pharmacy, Nirma University Page 5 Institute of Pharmacy, Nirma University Page 6 Institute of Pharmacy, Nirma University Page 7 Institute of Pharmacy, Nirma University Page 8 Institute of Pharmacy, Nirma University Page 9 Institute of Pharmacy, Nirma University Page 10 Institute of Pharmacy, Nirma University Page 11 Institute of Pharmacy, Nirma University Page 12 Institute of Pharmacy, Nirma University Page 13 Institute of Pharmacy, Nirma University Page 14 Institute of Pharmacy, Nirma University Page 15 Institute of Pharmacy, Nirma University Page 16 Institute of Pharmacy, Nirma University Page 17

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Publications and Presentations

1. Pyoderma Gangrenosum: A systemic Review of Incidence and Prevalence. “Journal for Clinical Studies”. Vol 7, Issue 1, 42-45.

2. Impact of vitamin d supplementation on lipid profile and clinical status in coronary artery disease patients. “Indian Journal of Clinical Practice”, Vol. 25, No. 10, March 2015.

3. Second prize in poster presentation entitled “Epidemiology and Vaccine development of Dengue fever” at National Conference of Infectious Diseases.

4. Article under communication:-Quality of Life assessment of oral cancer patients after mandibular resections using UWQOL (v4) Questionnaire: Reconstruction with Pectoralis Major Myocutaneous Flap.

5. Article Under communication:-Sleep Disorders and Quality of Life Assessment in the Elderly