"DETERMINATION OF QUALITY OF LIFE IN PATIENT WITH METASTATIC BREAST, LUNG AND COLORECTAL CANCER BEFORE, DURING AND AFTER ANTICANCER TREATMENT"

A Thesis Submitted to

NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

CLINICAL PHARMACY

BY

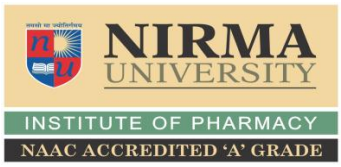
Ms. JHIL N. KADAKIA (14MPH701), B. PHARM.

Under the guidance of

Prof. JIGNA S. SHAH – GUIDE
Professor and Head, Department of Pharmacology

Dr. CHIRAG J. DESAI- HOSPITAL GUIDE
M.D., D.M. (Hemato-Oncologist), Consultant and Director,
Hemato-Oncology Clinic, Vedanta institute of medical science, Ahmedabad

Dr. DEEPA H. TRIVEDI- HOSPITAL GUIDE
M.D. (USA), Hemato-Oncologist,
Hemato-Oncology Clinic, Vedanta institute of medical science, Ahmedabad.



Department of Pharmacology
Institute of Pharmacy
Nirma University
Ahmedabad-382481
Gujarat, India.

May 2016

CERTIFICATE

This is to certify that the dissertation work entitled "Determination of quality of life in patient with metastatic breast, lung and colon cancer before, during and after anticancer treatment" submitted by Ms. Jhil Kadakia (14MPH701) 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 Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad, 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.

Hospital Guide

Dr. Chirag J. Desai
M.D. D.M. (Oncologist),
Director and Consultant,
Hemato-Oncology Clinic,
Vedanta institute of medical science,
Ahmedabad

Academic Guide:

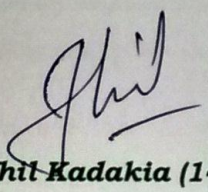
Prof. Jigna S. Shah
M. Pharm., Ph.D.,
Professor and Head,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University

Prof. Manjunath Ghate
M. Pharm., Ph.D.
Director,
Institute of Pharmacy,
Nirma University

Date: 26 May, 2016

DECLARATION

I hereby declare that the dissertation entitled "Determination of quality of life in patient with metastatic breast, lung and colon cancer before, during and after anticancer treatment", 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 Dr. Chirag J. Desai, Consultant and Director, Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad,. 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.



Ms. Jhil Kadakia (14MPH701)
Department of Pharmacology,
Institute of Pharmacy,
Nirma University,
Sarkhej - Gandhinagar Highway,
Ahmedabad-382481,
Gujarat, India

Date: 26 May, 2016

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Jhil Kadakia

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Abstract

Objective

In cancer, the body cells start dividing and spread into other nearby tissue. Breast cancer, lung cancer and colorectal cancer are the common cancer worldwide and nationwide. Quality of life is a standard of health, comfort and happiness experienced by an individual. Metastatic cancer is a life threatening disorder which is difficult to treat. Disease and/or treatment may affect psychology and emotions of the patients. Route of administration, stage, prior treatment, also affects quality of life of a patient. Thus the proposed study was an effort to elicit the actual quality of life by PRO (patient reported outcome) by patient himself.

Methodology

The proposed study was non-randomised, retrospective, prospective, single centric, observational study. Patients who were suffering from metastatic breast cancer, metastatic lung cancer and metastatic colorectal cancer were enrolled in the study. The questionnaire, EORTC QLQ-C30, BR23 (Breast cancer), LC13 (lung cancer) and CR29 (colorectal cancer) were filled up by patients at different time intervals i.e. before, during and after the anticancer treatment. We also compared quality of life between different routes of administration as well as between different treatment protocols. Basic characteristics such as Age, BSA, CBC, SGPT, RBS, CEA, alkaline phosphatase, serum creatinine were also analysed at different time interval. Statistical analysis was performed using two way ANOVA and Z-test.

Results

During the study, we screened 110 patients at Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad from these, 17 patients who refused to give written consent were not included in the study. Total 93 patients' were enrolled in the study and the data were analysed. Out of these 93 patients, 42 patients were suffering from metastatic breast cancer, 43 patients were suffering from metastatic lung cancer and 8 patients were suffering from metastatic colorectal cancer. In metastatic breast cancer overall functional score was better in after the anticancer treatment group, while oral treatment group showed better functioning when compared with IV treatment group. Other treatment group showed better functioning, but taxane group showed low scoring for function scale. For symptom score, during the treatment group showed

lesser symptomology as compared to other two groups except for upset by hair loss and systemic therapy side effect. In oral treatment group the symptomology were higher as compared to IV group. While in different treatment protocol comparison, the other treatment group showed improvement in symptom score. However, the global quality of life was almost same in all the groups.

Total 43 patients were enrolled in metastatic lung cancer, from which 33 were male and 9 were female. The function score was almost same at different time interval. While in oral group the functioning was bit higher as compared to IV group. The symptoms were decreasing throughout the study except for peripheral neuropathy, alopecia, fatigue, appetite loss, nausea vomiting, diarrhoea and pain in other parts of the body. Financial difficulties were increasing throughout the study. In oral group except for fatigue and pain in other parts of the body, the symptom score were decreasing. The global quality of life remained good in all the three group.

Total 8 patients enrolled in metastatic colorectal cancer, from which 6 were male and 2 were female. The overall functioning score was good in during the therapy group. Before the anticancer treatment the symptomology was high which got decreased in during the treatment group. Global quality of life was same in all the three group.

Conclusion

Overall, the quality of life was better in during the therapy group of all the three cancer. The scores for symptom and functional scales were changing throughout the study. We also found that the functional scale was better in oral group for all the cancers. However, the symptom scale was high in metastatic breast cancer and was decreasing in metastatic lung cancer.

Introduction

Cancer is a collection of diseases. In this, the body cells start dividing and spread into other nearby tissue, Cancer can began from anywhere in the human body. Generally, a cell in the human body starts growing and then divides into new cells according to the body's requirement. But as the age increases or any damages happen then they die and new cells takes place of them. When it starts growing, the whole process of cell growth breaks down, though the age increases or any damages takes place, the cell would not

die and continue to grow and divide and produces new cells and also affects surrounding cells may form growths called tumor.

There are various types of cancer. Major two types are solid tumors, which are mass of a tissue and blood cancer such as leukemias which do not form tumors. These tumors are fatal for the body. They can invade surrounding cells and as they grow, some of them can break down from the lump which trowels through the lymphatic system to other place in the body and over there it again starts growing and divides and makes another tumor. This process of spreading of disease from one part of the body to another part is called as “metastasis”

Other than cancerous tumor there is another type of tumor called as benign tumor. Which is non-malignant and do not invade other tissues. Unlike cancerous tumor, when they are removed generally they do not grow back. The root cause of the cancer is the change that happen in genes that manages the whole process of cell growth. Thus, it is called as a genetic disease.

The change in genes that cause cancer can be inherited by parents. Another cause for cancer is the environment; its exposure can change the gene sequences or can damage DNA which may affect cell growth process. This may lead to the cancer. Environmental exposure include chemicals, radiation etc. Individual person who have cancer are unique combination of genetic changes. As it grows, there are possibilities that additional changes may happen in that same tumor.[1]

According to WHO Global cancer facts and figure 2012, cardiovascular diseases are the primary cause of death worldwide (30%) and also in low-middle income countries (31%) as well as high income countries (38%). While cancer is the second most common cause of death worldwide (155) and also in high income countries (25%) and third common cause of death in low-middle income countries (12%).
For male worldwide lung cancer is the most common cancer, prostate cancer is the second most common cancer. And colorectal cancer is the third most common cancer. While in developed countries prostate cancer is the first common cancer and lung cancer is the second most common cancer. Colorectal cancer is the third most common

cancer. In developing countries, lung cancer remains the first common cancer but liver cancer and stomach cancer occupies the second and third position respectively.

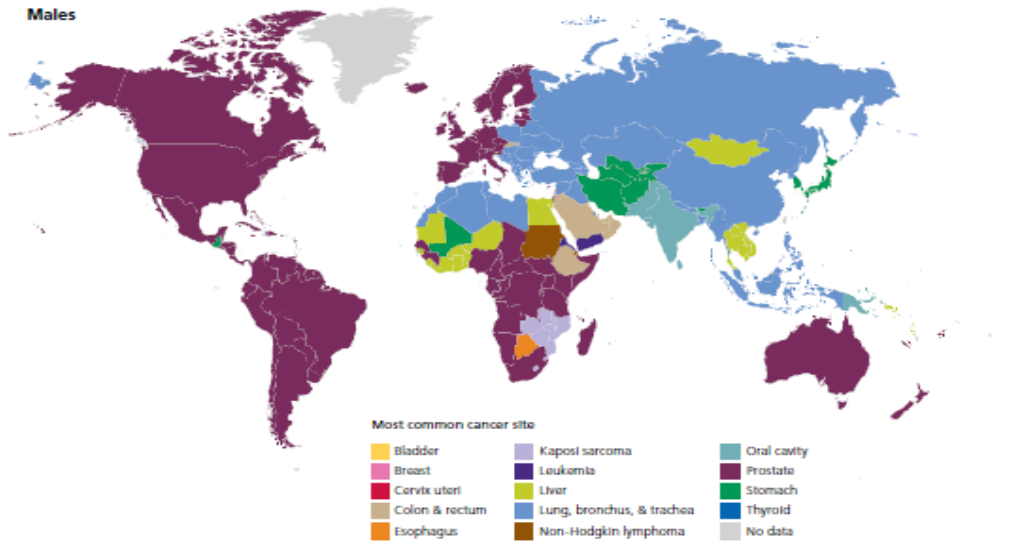


Figure 1: worldwide prevalence of cancer in male

For female, world wile breast cancer is the most common cancer, while colorectal and lung cancers are second and third most common cancer respectively. In developed countries the rank remains same as worldwide while in develop countries after breast cancer, cancer of cervix and uteri are second most common cancer and lung cancer is third common cancer. [2]

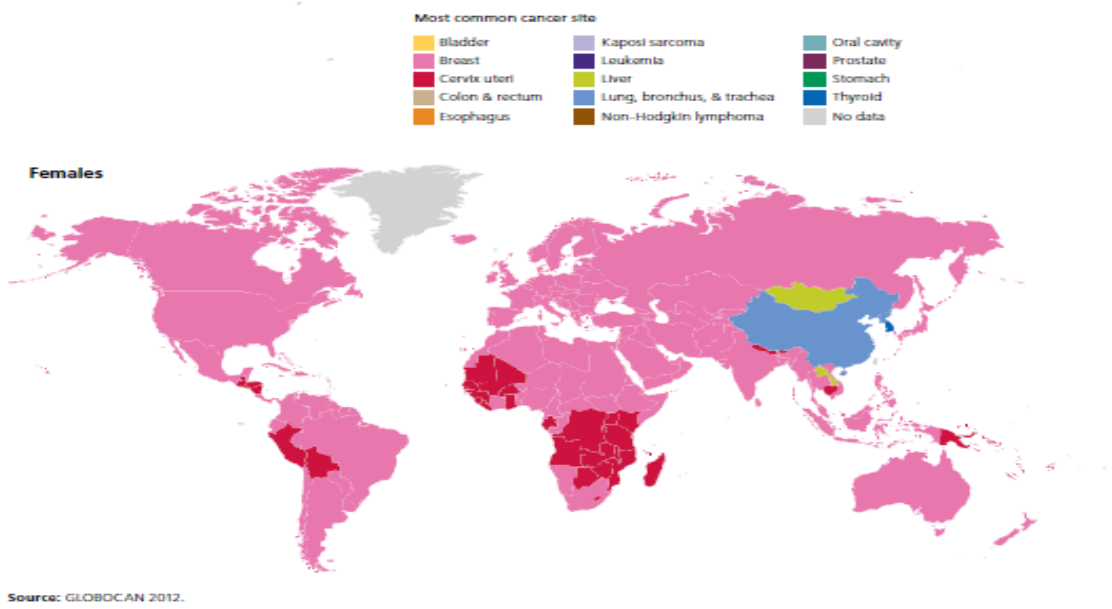


Figure 2: worldwide prevalence of cancer in female

According to WHO GLOBOCAN for the year 2012 the incidence of all the cancer for male in India for was 477482. While for female the rate was 537452. For male the mortality rate was 356730 and for female it was 326100. For the year 2015, the incidence of all the cancer in male was 514862 and for female it was 580727.. The mortality rate of all the cancer for male was 385052 and for female it was 354222.

In India, lip and oral cavity cancer is the most common cancer while for the female breast cancer is the most prevalent cancer. Lung cancer and colorectal cancer are the second and third most common cancer respectively. While for female cancer of cervix and colorectal cancer are second and third most common cancer respectively. [47][48]

Breast cancer is the most frequently diagnosed disease in women and is the most common cause of cancer death in women after lung cancer. It occurs in approximately 18% of all female cancers In India approximately 90,000 new cases estimated and 50,000 women are died due to this cancer.

The two challengeable variables which are associated with the occurrence of breast cancer are gender and age. For metastatic disease radiation therapy, surgery and chemotherapy are used together and may result in disease cure or palliation. [3][8]

Lung cancer is the leading cause of cancer death in both men and women. Lung cancer is mainly a disease of modern era. In India, approximately 63,000 new lung cancer cases are reported each year. The incidence of new cases of lung cancer ranges between 50 and 90 per 1,00,000 populations.

The overall 5-year survival rate for all types of lung cancer is approximately 15%.Cigarette smoking is responsible for most lung cancers. Smoking cessation should be encouraged, particularly in those receiving curative treatment Lung cancer is further classified into two sub class; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is diagnosed in most (80%) lung cancer patients. NSCLC has a slower growth rate and doubling time than SCLC [4][5][6][8]

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in men and third most common in women and third most common cause of cancer death. From a population perspective, age is the most important risk factor for CRC. CRC is a disease

of older individuals; 90% of cases are diagnosed over the age of 50-60. Clinical risk factors include dietary practices, genetic factors, familial syndromes, other pre-existing diseases, and advancing age approximately 70% of all colorectal cancers occur in the sigmoid colon and rectum. [7][8]

2. Cancer

Cancer is a group of diseases. It can originate from anywhere in the body and continue to grow and divide and can invade other surrounding tissues. Cancer is the second most common cause of death worldwide.[1]

2.1. Classification of cancer

Cancer can be classified in two ways, 1. By the type of tissue

2. by the location in the body [11, 8]

2.1.1. By the type of tissue

- **Carcinoma**

The origin of these types of cancer is the epithelial layer of the cells that separates one organ from another. It can be inner or outer side. This tissue is found throughout the body such as skin, gastrointestinal tracts etc.

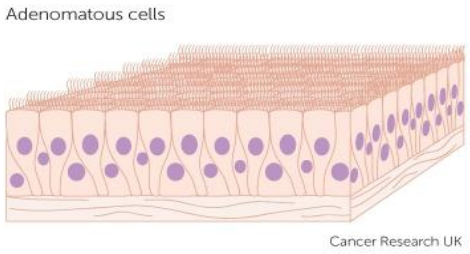
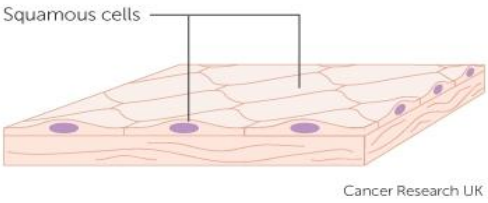


Figure 3a: Adenomatous cell

- **Adenocarcinoma**:

it originates in an organ such as breast, lung colon etc. or a gland such as thyroid gland, adrenal gland, etc. they generally occurs in the mucus membranes which looks like a white plaque



- **Squamous cell carcinoma**:

it originates from the squamous epithelium and occur in many areas of the body.

- **Transitional cell carcinoma**

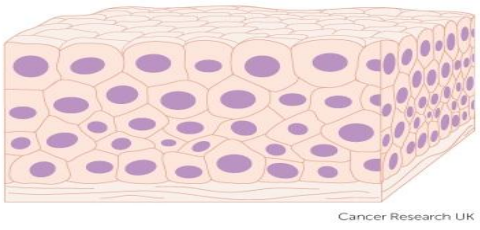


Figure 3c: Transdermal cell

These cells can expand as an organ expands, for example in the lining of the bladder cancer

- **Basal cell carcinoma**

They are found in the deeper layer of skin cells. They are uncommon cancer.

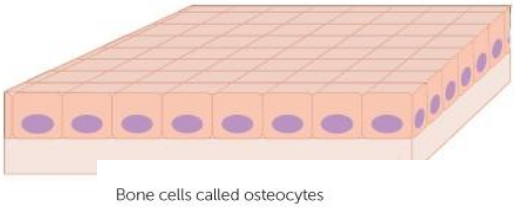


Figure 3d: Basal cell

- **Sarcomas**

It begins from the connective tissue which works as a support for the body. Bone tendon, cartilage, and fibrous tissue are included in the connective tissue. It is divided into two types; Bone sarcoma and soft tissue sarcoma such as cartilage sarcoma also known as chondrosarcoma and muscle sarcoma also known as rhabdomyosarcoma Chances of sarcoma are very less than carcinoma. In 100 cancer diagnosed, 1 case of sarcoma is there.

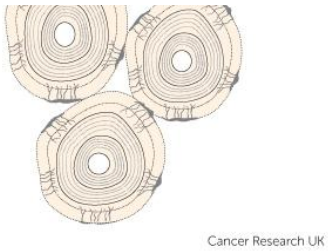


Figure 4a: Bone cells

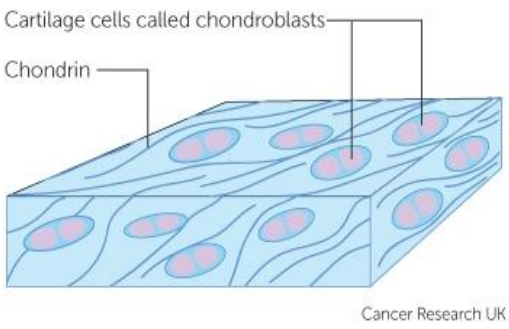


Figure 4b: Cartilage cell

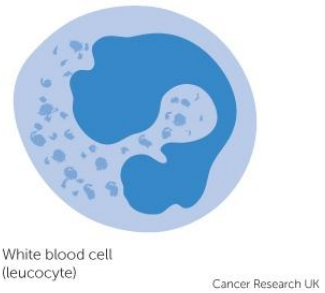
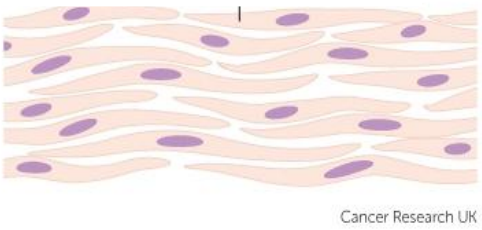


Figure 4c: muscle cell



Leukemia

It's a state where bone marrow produces white blood cells uncontrollably. And these cells are not grown completely thus not working properly to fight an infection. Leukemias are not much prevalent. The incident rate is 3 in 100 of all cancer cases but more prevalent in children.

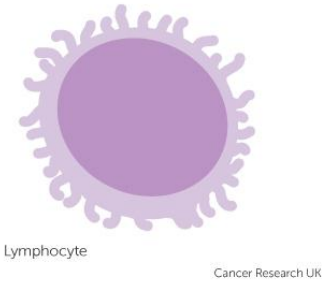


Figure 5: Leukocyte

Lymphoma

It starts from the lymphatic system. It's a system of tubes and glands in the body which filters out body fluid and fight for an infection. This system is made up of the spleen, lymphatic vessels and lymph gland.

Lymphoma can start from anywhere in the body because the lymphatic system runs throughout the body and in that some of the WBC starts growing abnormally and the keep on dividing. These cells don't die and they grow before they get mature.

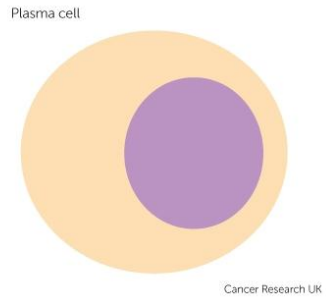


Figure 6: Lymphocyte

Myeloma

It is also called as multiple myeloma. This type of cancer starts in a type of plasma cell called as WBC. They produce immunoglobulin (antibody) to fight against infection. In this type of cancer plasma cell grows abnormally and multiplies uncontrollably and produces one type of immunoglobulin which does not work to fight thus making immune system weak.

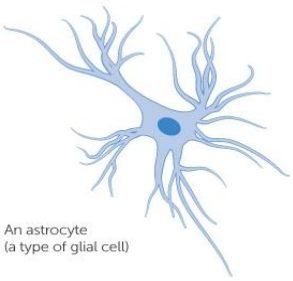


Figure 8: Glial cell

Brain and spinal cord cancer

Our body is controlled by the brain which sends electrical messages through nerve fibres. The fibres go out of the cerebrum and join together to make the spinal cord, which also takes messages from the body to the brain. The brain is made up of millions

of cells called as neurones which contains special type of cells called as glial cells which works as a support for nerve cells. The common brain tumors are produced in glial cells such as glioma, glioblastoma.

2.1.2. By the location in the body

Classification is as follows

i. Stage I T1 N0 M0
ii. Stage IIa T0-2 N0-1 M0
iii. Stage IIb T2 N0-1 M0
iv. Stage IIIa T-3 N0-2 M0
v. Stage IIIb T1-4 N1-3 M0
vi. Stage IV T4 any N M1or higher

Where, T= number of Tumor, N= Number of Nodes involved and M= number of Metastasis.

2.2. Metastatic Breast Cancer (MBC)

Breast cancer is a heterogeneous group of neoplasm originating from the epithelial cells lining the milk ducts and it is the most common malignancies, which causes18% of all female cancer deaths worldwide,

According to medical experts, in India, about four out of five breast cancer patients are at an advanced stage when they got diagnosed. It is the first most common cancer among women in India which accounts for 7% of global burden and one-fifth of all cancers among women in India. In India approximately 90,000 new cases estimated and 50,000 women are died due to this cancer.

The two challengeable variables which are associated with the occurrence of breast cancer are gender and age. The treatment of breast cancer varies by disease stage at diagnosis and patient- specific prognostic factors.

For metastatic disease radiation therapy, surgery and chemotherapy are used together and may result in disease cure or palliation. Non-invasive breast cancer is generally easily controlled with surgery alone or surgery plus radiation

The goals of treatment for metastatic breast cancer are to prolong survival and palliate symptoms. The choice of therapy depends on the site of disease involvement and patient

characteristics. Although patients with metastatic breast cancer will most likely die of their disease, many patients can achieve durable responses to treatment that allow them to lead prolonged lives with good quality

Early-stage breast cancer (stages I and II) is managed with breast-conserving surgery and radiation. Adjuvant hormonal therapy or chemotherapy is indicated.[8][3]

2.2.1. Clinical presentation

The patient may not be having any symptom as a breast cancer but during rotini check-up they may get diagnosed. [8, 12]

The possible symptoms for early stage breast cancer are as follows

- A painless, palpable lump
- Change in size or shape of breast
- Nipple discharge, skin thickening, oedema, skin dimpling
- Palpable local or regional lymph node

For the metastatic breast cancer following symptom may be included in the above one, depending on the site of metastasis the symptom may vary

- Bone pain
- Difficulty in breathing
- Abdominal pain or enlargement
- Change in mental status

2.2.2. Diagnosis [8][13]

The series of tests are required to get complete idea regarding the possible diagnosis. The primary examination is physical examination, family history. If any of the family member had breast, ovary, uterus, cervical cancer then there are chances to have the same. On the basis of physical examination further tests are recommended

Following tests are used to diagnose breast cancer

- **Imaging test**

1. **Mammography**

It’s a X-Ray that allows one to examine the breast tissue. in these the pictures are taken from different angles.

2. **Ultrasound**

It uses high frequency waves. With the help of that it creates an image of a tissue. It has the ability to differentiate\between solid mass and fluid filled cyst which is not a cancer.

3. **Magnetic resonance imaging (MRI)**

It uses magnetic field to create a detailed image of the human body. It can also measure the tumor size. A contrast medium which is dye is given to the patient before scanning by IV route which works as a marker and with the help of that the image is generated.

4. **Computed tomography (CT or CAT) scan and Positron emission tomography (PET) scan:**

Both of them are used to detect the tumor outside the organ. Both create 3D structure of the tumor. In PET scan radioactive substance is administered. These substances are absorbed by the cells that require higher energy. Thus the tumor and if the metastasis is there then it can also be detected. They both can be used to determine the exact size and location of the tumor.

- **Biopsy**

It’s a removal of small amount of the tissue to study under the microscope. It gives a clear idea about the disease. Then it is analysed. There are different types of biopsy.
A fine needle aspiration is used to take small amount of tissue. A core needle biopsy uses big needle to remove large amount of sample. A vacuum assisted biopsy is also used to remove large amount of sample.
After the analysing the sample the report is generated which gives detailed idea about the disease. Tumor features, grade of disease, type of tumor, receptor sensitivity etc. on the basis of the treatment is decided.

- **Blood tests**

1. **Complete blood count (CBC):** It gives idea about the number of different cells present in the blood. On the basis of which any abnormality is there or not can be detected.

2. **Serum chemistry**: It is used to check electrolyte abnormality. Liver function tests such as alkaline phosphatase, SGPT, SGOT, etc. are used to detect whether the cancer has spread or not.
3. **Hepatitis test**: It is used to check whether there is any prior exposure of hepatitis.
4. **Blood tumor marker:** they are tumor proteins present in the blood. They are generally not recommended in early stage as it would not be that accurate.

2.3. Metastatic Lung Cancer (MLC)

Lung cancer is the leading cause of cancer death in both men and women. Lung cancer is mainly a disease of modern era and perhaps one of the most important health issues today. According to National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) 2012 report, lung cancer is the first most common cancer worldwide and it is the most common cause of cancer death worldwide according to various epidemiological studies Indian population has higher prevalence of lung cancer as compared to western countries. In India, 63,000 new lung cancer cases are reported each year.

The incidence of new cases of lung cancer ranges between 50 and 90 per 1,00,000 population. The overall 5-year survival rate for all types of lung cancer is 15%. Cigarette smoking is the major cause for lung cancer.

Lung cancer is classified into two sub classes; non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC). NSCLC is diagnosed 80% lung cancer patients. NSCLC has a slower growth rate and doubling time than SCLC NSCLC is not as aggressive as SCLC and is classified into large cell carcinoma adenocarcinoma and squamous cell,. SCLC is an aggressive and rapidly proliferating tumour.

The most appropriate treatment for NSCLC is determined by the size and location of the tumour, extent of lymph node spread, presence or absence of metastatic sites, and the performance status of the patient. Surgery and adjuvant chemotherapy are the choice of treatment for early stage NSCLC.

In patients with locally advanced NSCLC (stage III), chemotherapy with or without radiation followed by surgery improves survival over radiation followed by surgery [4-6, 8]

2.3.1. Clinical presentation [8, 14]

Sing and symptom are as follows

- Cough
- Haemoptysis
- Dyspnoea
- Chest-arm shoulder pain
- Wheeze and stridor
- Pleural effusion
- Dysphagia
- Hoarseness
- Horner's syndrome
- Pericardial effusion

Sign and symptom of metastasis

- Bone pain
- Liver dysfunction
- Neurological defect
- Spinal cord compression
- Weight loss
- Clubbing
- Anaemia

2.3.2. Diagnosis [8, 14]

The techniques that are used for diagnosis of lung cancer are same as that of breast cancer.

Chest X-Ray:

It's a first test that is used to diagnose any lungs relates problem. It is not accurate test as it cannot distinguish between cancer tumor and absences.

PET-CT scan

It uses X-Ray as well as computer to create an image of a tumor. It can also measure the size of the tumor. Evan after treatment change in the size of tumor can also be observed.

Bronchoscopy and biopsy

If the CT-Scan shows any abnormality then to confirm what type of cells are they and to get detailed idea bronchoscopy is done in which a thin tube is passed through mouth or nose to lungs to get small sample of the tissue which will be examined under microscope. After the examination it will tell the grade of disease, receptor sensitivity, etc.

2.4. Metastatic Colorectal Cancer (MCRC)

Colorectal cancer (CRC) is a disease with a major worldwide burden. It is the third most prevalently diagnosed cancer in men and fourth most common in women. Worldwide it is the third most common cause of death, responsible for 639,000 deaths annually.

Among all the factors, age is the most important risk factor for this cancer. Predominantly it is a disease of older peoples; 90% of cases are diagnosed over the age of 50-60.

Clinical risk factors include dietary practices, genetic factors, familial syndromes, other pre-existing diseases, and advancing age. Approximately 70% of all colorectal cancers occur in the sigmoid colon and rectum. While in other parts, the incidence is in decreasing manner: the ascending colon (16%), the transverse colon and splenic flexure (8%), and the descending colon (6%). Histologically, adenocarcinoma accounts for 90% to 95% of colorectal tumours. The remaining 5% to 10% of large bowel tumours are squamous cell carcinomas, undifferentiated carcinomas, rectal characinoid, or, very rarely, sarcomas.

The treatment goal for stages I, II, and III colon cancer is cure; surgery should be offered to all eligible patients for this purpose and overall mortality as compared to observation alone in patients with stage III disease.[7, 8]

2.4.1. Clinical presentation

Symptoms of patients are generally non-specific, they may vary in individuals. However, the common symptoms are as follows. [8, 15]

- Change in bowel movements
- Constipation
- Nausea, vomiting
- Abdominal discomfort
- Fatigue
- Hepatomegaly and jaundice in an advance diseases.
- Leg oedema
- Weight loss
- Pain in lower back
- Blood in stool

2.4.2. Diagnosis [8, 15]

Colonoscopy:

It's a method to that allows one to look inside the colon and rectum of patients and it captures images of tumor or abnormal part for further process.

Biopsy:

It's a removal of small part of a tissue to examine under the microscope for the exact detail of a disease. It can be performed during the colonoscopy.

Blood tests

1. **Complete blood count** is done to check different cell counts and any blood related abnormality.
2. **Biochemistry:** This is especially useful to check whether other organs are working normally or not. In case of metastasis for example liver metastasis is there then the serum alkaline phosphatase level changes indicating liver dysfunction.
3. **Blood tumor markers:** Tumor markers are the tumor protein which is different than normal protein thus higher level of these markers indicates severity of disease, for example Carcino Embryonic antigen (CEA).

PET and CT scan:

These are the tests that are used to measure the size and location of a tumor. They use X-Rays and computer together to generate an image. In PET scan, dye is injected to the patient's vein, which will be absorbed by the tissues that requires higher energy then can be detected by a scan in which the tumor gets highlighted.

Chest X-Ray:

It's a first test that is used to diagnose any abnormality It is not accurate test as it cannot distinguish between cancer tumor and absences.

Ultrasound:

It uses high frequency waves. With the help of that it creates an image of a tissue. It has the ability to differentiate\between solid mass and fluid filled cyst which is not a cancer.

2.5. What is quality of life?

It is the standard of health, comfort, and happiness experienced by an individual. Quality of life (QoL) is a pervasive concept that has different philosophical, political and health-related definitions. Health-related QoL (HRQoL) includes the physical, functional, social and emotional well-being of an individual [23]

It is a board concept that includes the assessment of positive and negative aspect of life.[17] The concept and assessment of HRQoL has emerged since the 80s this concept has covered the purpose of overall quality of life that affects both physical and/or mental health. [18-21]

For an individual the HRQoL includes the mental and physical health which describes their perception for health related problems and conditions, financial difficulties, social status, cognitive functioning and health related symptoms. For the community the concept is different. For them it includes different policies and practices that affect public's health related knowledge, resources available, financial status, conditions. [22]

HRQoL asks about the physical, mental health and function that is gained by an individual which has become an important aspect of health surveillance. It is considered valid for the indication of needs of service and outcome of interventions. Self-assessment of health related problem is found to be more potent predictor of morbidity and mortality than other objects. [24, 25, 16]

2.6. Quality of Life and Cancer

Metastatic cancer is a life threatening disorder which is difficult to treat. Among all of the cancers, lung, breast and colon cancers are the common type of cancer and it has highest morbidity and mortality rate. For the treatment of metastatic cancer, different type of anticancer treatment is given. This treatment acts on fast growing cells of the body and destroys them, thus it also affects non-tumour normal cells such as hair cells, nail cells, WBC, mucosal cells etc. This can lead to unintended, sometimes

serious side effects. These side effects also affect the psychology and emotions of the patients and contribute to quality of life.

Routes of administration also could affect patient's quality of life.

Not only anticancer treatment but stage and prior treatment of the disease also affect their quality of life. Anticancer treatment can hold disease progression but cannot cure metastatic cancer completely. So the quality of life before therapy, during therapy and after therapy can be different. When treating an incurable disease, it is essential to ensure that the quality of life does not deteriorate. Neither by disease and nor by its treatment.

By giving anticancer treatment we intend to control cancer by inducing response. We assume if the tumor shrinks i.e. if tumor responses to anti-cancer treatment the patient's symptoms will improve and hence the quality of life will improve. Sometimes because of the effects of the drugs, in spite of the tumor responding, the quality of life may not improve or deteriorate, it has been for long debated who would assess the QOL in the patients, whether the healthcare provider or patient himself?

The tumor response should be assessed by the healthcare provider, but the best way to assess QOL is as narrated by the patient himself. This fact is often overlooked by healthcare providers

In previous years till mid 80s the value of effect of chemotherapy was measured by the patients' quantity of life. Now the understanding and the concept of measurement has changed in the health services. For the measurement of therapeutic effect, patients' own perception should be considered as a main factor. [25]. More even quality and quantity of life as well as the cost of the treatment should also be included. An article written by an author in 1971 suggested that survival time or quantity of life was a single factor of the total problem and it is not necessary that it is related with how well patient is doing in either of all the factors. [26]

Despite of toxicity and side effects it should be noted that these patients however chooses anticancer treatment. [27-29]

In clinical trial, the measurement of quality of life has also been incorporated with the ambition to know actual health related problem and to serve as an endpoint such as

tumor response, survival, physician's concern regarding patient's status, freedom from relapse. [30]

As the dose of the treatment increases, the incidence of side-effects also increases. It is increasingly recognised that measurement of patients' subjective tolerance to treatment, physical, functional and emotional well-being, and the symptom status, during and following therapy is vital. [32]

When the benefits of chemotherapy are potentially great, i.e. with probable or possible cure as a result, the costs for treatment and the side-effects that treatment may involve are conceptually easier to accept for both the patient and the health services. When the potential benefit of treatment is less conspicuous, the acceptance level of side-effects also declines [31]

Thus the proposed study was an effort to elicit the actual quality of life by PRO (patient reported outcome) and should help the healthcare providers in determining what patient wants.

There are number of questionnaires which helps one to measure the quality of life in cancer patients such as, The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC-QLQ, Functional Assessment of Cancer Therapy (FACT), The Cancer Rehabilitation Evaluation System (CARES), and The Functional Living Index Cancer (FLIC). From all of these EORTC is very common and specific questionnaire which is available in so many languages and easy to interpret.

The European Organisation for Research and Treatment of Cancer (EORTC) was founded in 1962. It is an international non-profit organisation. The purpose of this organization is to conduct, develop, coordinate and stimulate cancer research in Europe with the help of oncologists and scientists.

The EORTC quality of life questionnaire (QLQ) is a system which measures the health related quality of life (QOL) of cancer patients. The QLQ-C30 is the output of collaborative research done for several years by the group of specialists. It was released in 1993. It has been used by a large number of researchers for the measurement of QOL in different type of cancer; also been used in various other, non-trial studies.[33]

2.7. Review of literature

2.7.1. Breast cancer

- The findings of study carried out by Montazeri, et al (2008) suggested that there were deteriorations in patients' scores for body image, sexual functioning and significant improvements for breast symptoms, systematic therapy side effects and patients' future perspective. They also found significant change in function and global quality of life. [34]
- Another study carried out by Leng, et al. (2014) suggested women with breast cancer had good quality of life during their first 4 years of survivorship and had significant concern over the financial impact of breast cancer.
- Also found that younger women had experienced more physical and psychosocial concerns than older women and validated that EORTC questionnaires are very much useful in interpreting quality of life [35]
- Montazeri, et al (2000) suggested that functional and symptoms scales changes over time, as a function of a patients' performance status changes and also indicated that the EORTC questionnaire are reliable[36]
- A state-wide population based cohort study done in Germany by A. Waldmann et al (2007) for the measurement of quality of life in breast cancer showed that the overall quality of life was high in the female though the patients were more concerned about their financial difficulties. [37]
- Study done by Lee et al (2007) found that the patients who didn't completed of treatment were having poorer quality of life as compared to the patients who completed the therapy. The post treatment group showed very poor score for role, cognitive and social functioning. For the symptom scale they were also concerned about fatigue and financial difficulties. They also found that the higher score of overall quality of life was related to the satisfactory medical care, completion of treatment, being involved in decision making process, overall good health before surgery.[38]

2.7.2. Lung cancer

- Bergman, et al (1994) showed that EORTC QLQ-LC13 as a clinically justifiable and useful tool for measuring disease and treatment based

symptoms in lung cancer patients also mentioned that all item scores changed significantly i.e. treatment toxicities increased and lung cancer symptoms decreased.[39]

- Another study carried out by Chie, et al (2004) suggested that patients in the follow-up group (2nd line) revealed higher scores of quality of life, and lower scores of nausea/vomiting also physical functioning[40]
- Osoba, et al (1994) performed a study on breast cancer and lung cancer suggests QLQ-C30 shows reasonable psychometric properties and it came out to be responsive to the effects of chemotherapy and metastatic disease. It differentiate moderately well between different stage of diseases [41]
- Study carried out by cheng et al (2003) concluded that the quality of life in patients with lung cancer was worse as compared to the reference value. The patients with lower income and/or education had poorer quality of life, while young male and married patients had higher quality of life. Non-small cell lung cancer patients had better quality of life as compared to small cell lung cancer patients. Patients with last stage or metastasis had worse quality of life. They also reported that the treatment could decrease the quality of life.[42]
- Result of a study done by Wintner (2013) to measure the quality of life during chemotherapy in lung cancer patients reviled that irrespective of chemotherapy all the patients showed the stable quality of life. Patients receiving 3rd line or above palliative treatment had worn QOL while patients receiving 1st line treatment had better QOL as compared to above.[43]

2.7.3. **Colorectal cancer**

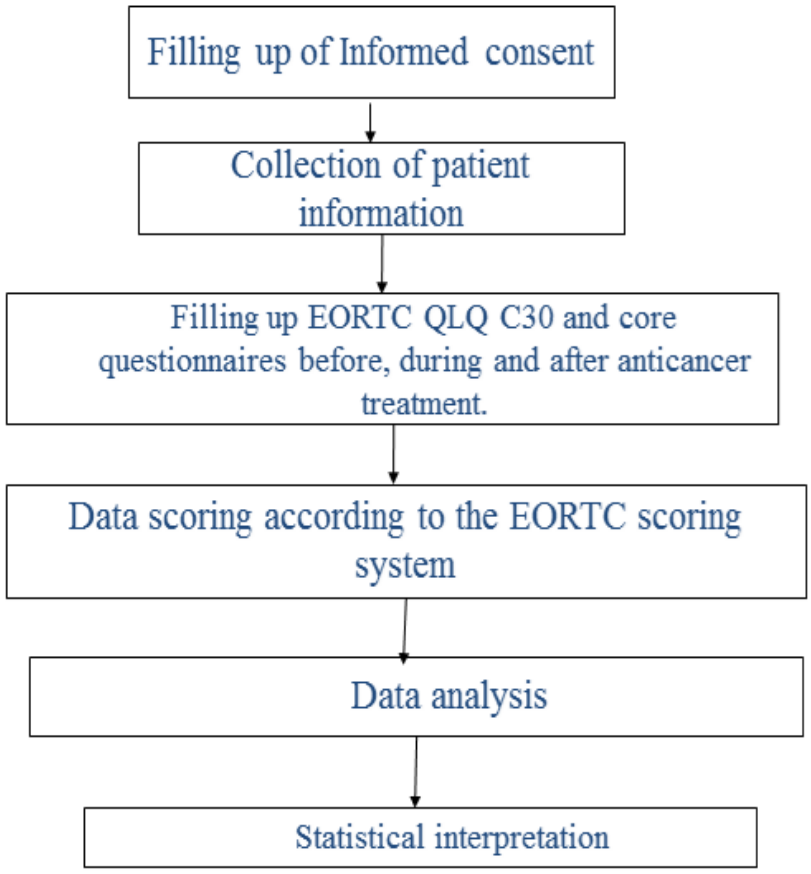
- Study carried out on advanced colorectal patient by Urdaniz, et al (2006) suggests that patients receiving treatment had higher score for functional capacity and low scores for toxicity which suggests an adequate control on chemotherapy side effects
- It confirms that Quality of Life of patients receiving treatment were in appropriate situation to receive it. And also stated that a significant number of patients have tolerated the chemotherapy treatment [44]

- In a study carried out by Bang, et al (2005) for the palliative treatment suggests decreased symptoms such as pain and sleep disturbance. Significant improvement was noted in functional scale but the effect did not persist throughout the course. The anxiety scores decreased throughout the period of intervention [43]
- Alabbas et al (2015) carried out a study on impact of various factors on colorectal cancer, which concluded that majority of patients were having pain. Mpst of the male patients had abdominal cramps and diarrhoea and half of the total patients reported good appetite. The overall quality of life was good in all the patients. [46]

Very scanty data are available on measurement of quality of life in cancer patients in India. Keeping this insight we designed a single centric, retrospective, prospective, non-randomized study. This study will help care givers, researchers and people to understand health related problems in these patients.

4.1. Study design

- The proposed study was e a single centric, non-randomized, retrospective and prospective observational study.



4.1.1. Site of study

- Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad.

4.2. Study population

- Age eligible for study: No limitation
- Gender eligible for study: Both
- Sample size: Estimated sample size for each metastatic cancer was 30.

4.2.1. Inclusion criteria

- Adult male and female patients of age more than 18 years
- Patients having either metastatic breast cancer or lung cancer or colon cancer
- Willing to give written informed consent

- Those who have been on anticancer treatment or those who were planned to receive anticancer therapy at Hemato-Oncology Clinic, Vedanta Institute of Medical Science.

4.2.2. Exclusion criteria

- Do not have metastatic cancer.

4.3. Ethical consideration

Study protocol was reviewed and approved by the ethics committee of Care Institute of Medical Science (CIMS), Registration no: ECR/206/lnst/GJl2o13, 9th July 2015.

4.4. Length of study

- Approximately 6 months

4.5. Evaluation criteria

- Those who were fulfilling the inclusion and exclusion criteria and those who were willing to give informed consent were included in the study. Following points were measured during the study
    - The QLQ-C30 questionnaire was filled up by the patient at the day 0 i.e. on the day of diagnosis or before anticancer treatment, during the treatment and after the completion of anticancer treatment.
    - The collected data were measured and compared for the change in quality of life.
    - Correlation between disease and various factors like age, sex, stage of disease, prior treatment, co-morbidities, and route of administration were measured.
    - Laboratory tests:
        - Complete Blood Count (CBC)
        - Serum Glutamic Pyruvic Transaminase (SGPT)
        - Serum Creatinine,
        - Alkaline phosphatase
        - Random Blood Sugar (RBS)
        - Carcino Embryonic Antigen (CEA)
        - Data of PET Scan and CT Scan

4.6. Statistical Analysis

- Analysis was done using Graph pad Prism (Version 6) and Microsoft Excel 2010. Quantitative results were expressed in terms of mean ± SEM. And Mean±SD,
- We performed Two way ANOVA and Z-test for statistical analysis

4.7. Research method

4.7.1. Study design

- This was a single centre, non-randomised retrospective and prospective observational study. This study examined the quality of life of metastatic cancer patients. Informed consent was signed by the patients before collection of patient information. The measurement was done by filling the EORTC QLQ C30 and core questionnaire. The collected data were analysed and scored according to the EORTC scoring system.

4.7.2. End of study

- The end point of study was completing the anticancer treatment and QOL questionnaire at appropriate time point.

4.7.3. Data collection

- Data collection was done on the day when patient came for regular treatment or follow up for retrospective patients.

4.7.4. Population

- Patients will be selected randomly those who fulfil the study requirement. Statistically it is estimated that approximately total number of patients in metastatic breast cancer, lung cancer and colon cancer would be 384, 382, and 381 respectively. Recruitment will continued beyond this point after getting approval of ethics committee.

4.8. Data management

4.8.1. Data confidentiality

- All the data related to the patient were kept confidential and under controlled access.

4.8.2. Data collection

- EORTC QLQ C30 and core questionnaires were filled up by patient before, during and after the anticancer treatment. Scores were given according to the EORTC scoring system. Statistical analysis was done and its significance was measured.

4.8.3. Data analysis

- It was done using EORTC QLQ scoring system.

4.9. Protection of human subject

4.9.1. Responsibility of investigator

- The protocol and informed consent form was reviewed and approved by the ethics committee before study start. Prior to the study start, investigator signed protocol signature page confirming he/she was ready to conduct study. Any study related problem was informed to ethics committee within 24hr.

4.9.2. Informed consent procedure

- Eligible patients who fulfilled the protocol requirement were required to sign inform consent form approved by ethics committee. In case where the consent was signed by patient's representative, patient must be informed about study as much as he/she can understand. The form contains details about the study and it says that the patient is ready to undergo study and all the data obtained will be used in research but all the data are confidential, which will only be given to third party without authentication.

4.9.3. Discontinuation of study

- Study can be discontinued if any problem occurs.

4.9.4. Publication of study protocol and result

- After finalization of the study report, result will be submitted for publication in a journal.

4.9.5. Confidentiality of study document and patient record

- Confidentiality was ensured by the investigator. Patients were not identified by his/her name in any document.

3.1. Aim

- The main aim of the study is to measure the quality of life in patient with metastatic breast, colon or lung cancers that are being treated with an anticancer treatment.

3.2. Objectives:

3.2.1. Primary Objective:

- To evaluate quality of life using EORTC QLQ C30 and core in patient suffering from metastatic breast cancer, lung cancer and colon cancer before, during and after anticancer treatment.

3.2.2. Secondary Objectives:

- To compare QOL between oral and parenteral treatment.
- To compare side effects of different drugs by different route of administration; parenteral vs. oral.
- To evaluate quality of life with respect to combination drug therapy and monotherapy.

5. Results

In present study we enrolled 93 patients from which 42 patients were suffering from metastatic breast cancer, 43 were suffering from metastatic lung cancer, and 8 were suffering from metastatic colorectal cancer

5.1. Metastatic Breast Cancer

5.1.1. Demographics

The Metastatic Breast Cancer patients were divided into four groups before, during, after and oral based on routes of administrations. We also analysed the patients data based on different treatment protocol. Taxane based group, Adriamycin based group and other treatment group. In other treatment include gemcitabine, carboplatin, trastuzumab, vinorelbine. The number of patients enrolled in the each group and the demographics are listed in following tables.

patient was 51 years. The body surface area decreased during the therapy and again got increased after the therapy. The random blood sugar (RBS) was found to be increasing throughout the study. The CBC, SGPT, Serum. Creatinine and alkaline phosphatase were within the range of all the patients.

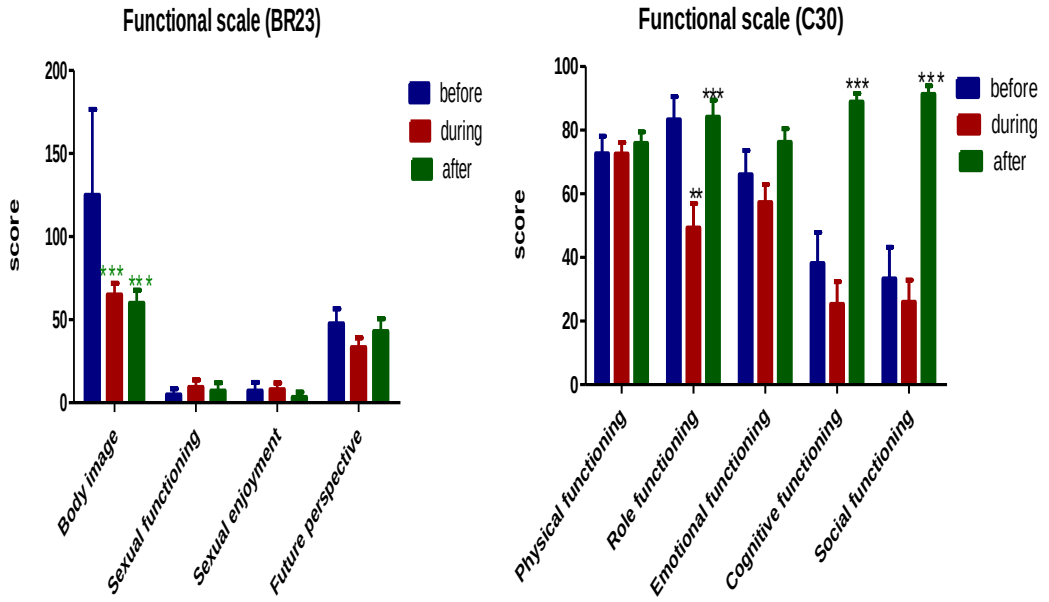
5.1.2. Function score

Comparison of data at different time interval

Table number 5.1.5. shows the functional score of the breast cancer patients. The functional score represents the level of healthy functioning of an individual. Higher the score, higher will be the functioning. The body image score was high in patients before the treatment, which got significantly decreased in during and after the treatment. In sexual functioning and sexual enjoyment many scores were missing because the patients were not feeling comfortable in answering the questions. Future perspective parameter indicates the worry for the future that how my health is going to be, what is going to happen in future with my health in context of the cancer. In our study the score was insignificantly high in the patients before the therapy, which got reduced during the therapy and again increased after the therapy.

Having problem in physical functioning means problems faced by the patients due to disease or treatment while performing physical work. The score was almost same in all the three groups. Role functioning indicates the role they play in their daily routine activity which was higher in before the treatment group and got decreased in during the treatment group and again got significantly increased in after the treatment group. Emotional functioning indicates the behavioural changes such as irritation, worry and depression related to financial difficulties, disease or treatment, etc. The emotional functioning was found to be lower in during the treatment group. Cognitive functioning indicates remembering past scenes or concentrating for a particular task. The score was significantly higher in after the treatment groups as compared to the other two groups. The social functioning includes the family life as well as social life. In the before and during the treatment groups, the social functioning score significantly was low as compared to the after the treatment group.

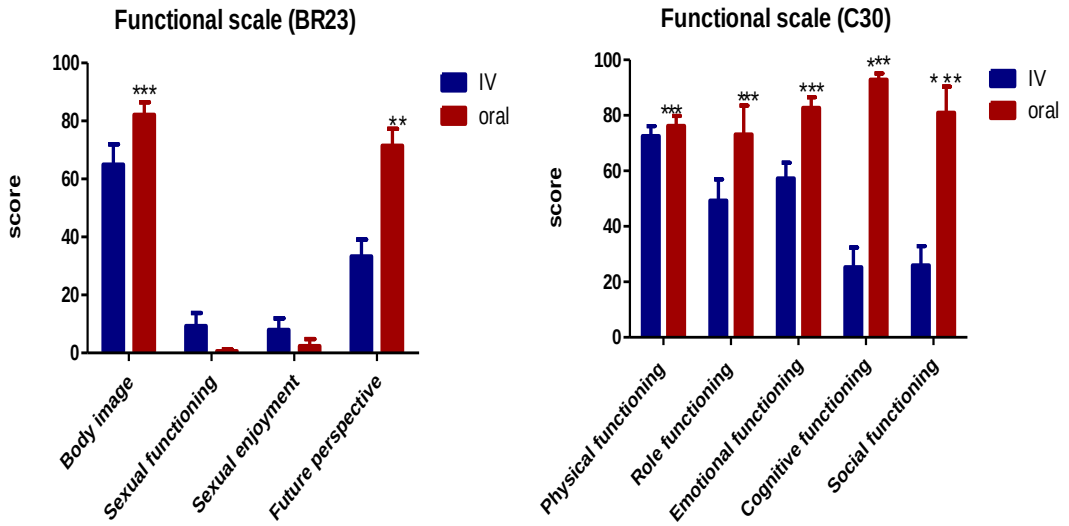
Figure 5.1.1 Functional score at different time interval



Comparison of data between different routes of administration

In our study, we compared quality of life between different route of administration i.e. Oral vs. Parenteral. The body image function score was significantly higher in the oral treatment group as compared to parenteral group. For sexual functioning and sexual enjoyment, patients were not feeling comfortable to answer the questions. For future perspective again the score was significantly high in oral treatment group. Physical function, role function, emotional function, cognitive function and social function, all of these function scores were significantly higher in oral treatment group as compared to parenteral group.

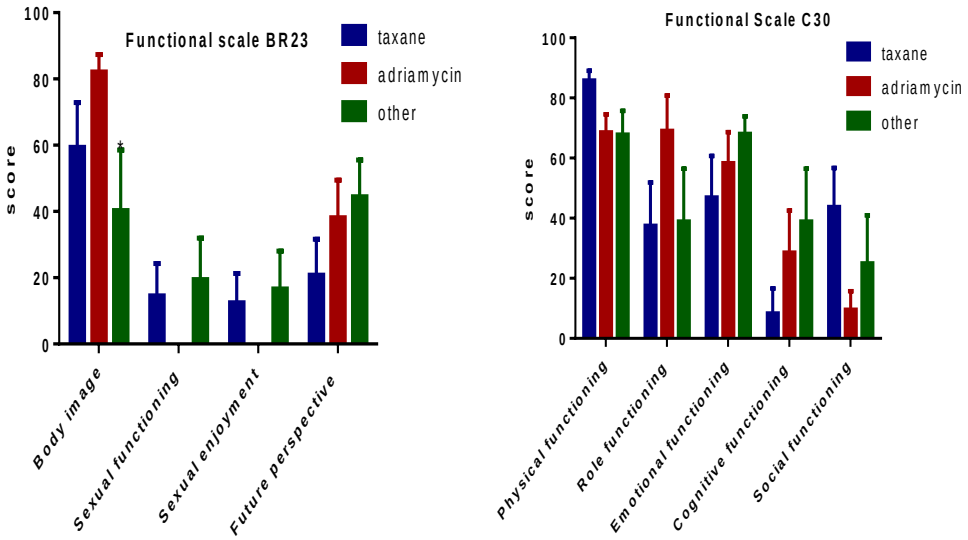
Table 5.1.2. Functional score in different routes of administration



Comparison of data between different treatment protocols

We also compared different treatment protocols: 1. Taxane based treatment protocol, 2. Adriamycin based treatment protocol, 3. others, where in gemcitabine, carboplatin, trastuzumab, vinorelbine drugs were administered. For functional score, the body image function was significantly higher in adriamycin group as compared to taxane group, while in other treatment group the function got significantly decreased as compared to other two groups. Future perspective score was significantly higher in other group. Physical functioning was high in taxane based group. While role functioning was significantly higher in adriamycin based group. Emotional and cognitive functioning were higher in other treatment group wile in Adriamycin based group the cognitive behaviour was higher. Social functioning was higher in taxane based treatment.

Figure 5.1.3. Functional score of the different treatment group.

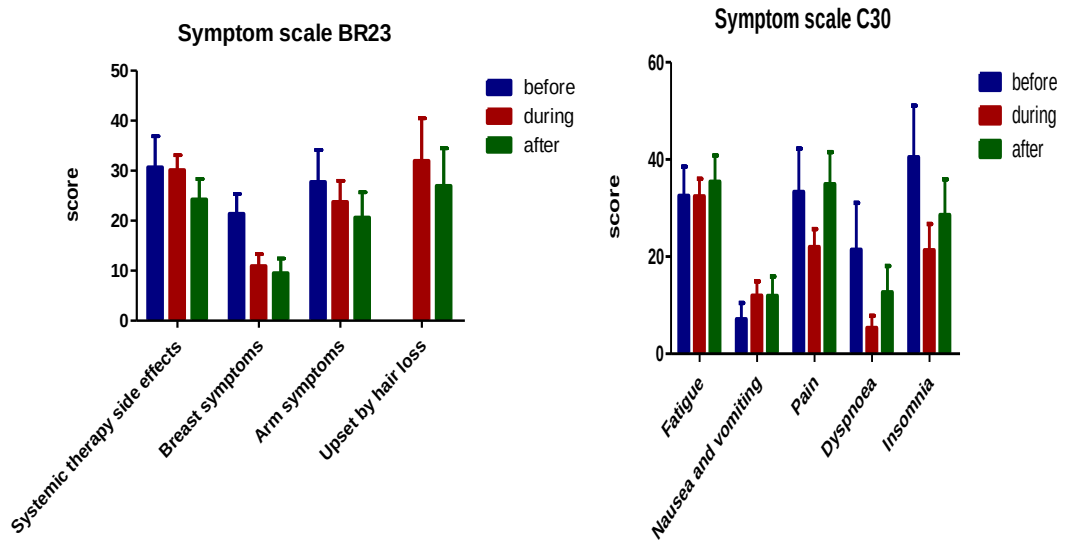


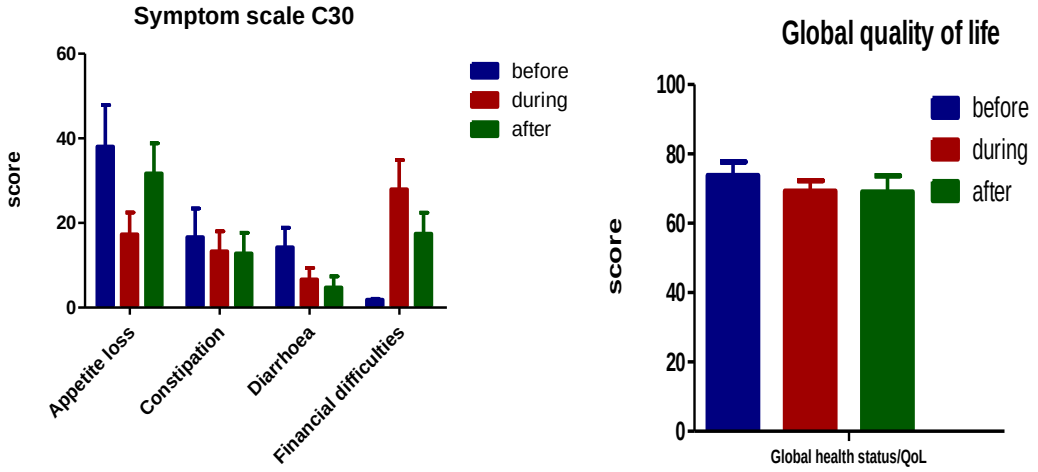
5.1.3. Symptom Score and Global quality of life

Comparison of data at different time interval

Symptom scores are the manifestation of a disease or treatment, while global quality of life represents overall health of an individual. As the symptom score increases, the symptomology or problem increases, while for global quality of life, higher score represents better QoL. The systemic therapy side effect score was same in before and during the treatment group which decreased in after the treatment group. All the symptoms listed in the following table 5.1.8,.insignificant change in symptomology were noted. In global quality of life also no significant change was found. The overall health was good in all the three groups.

Figure 5.1,4, Symptom score and global quality of life at different time interval

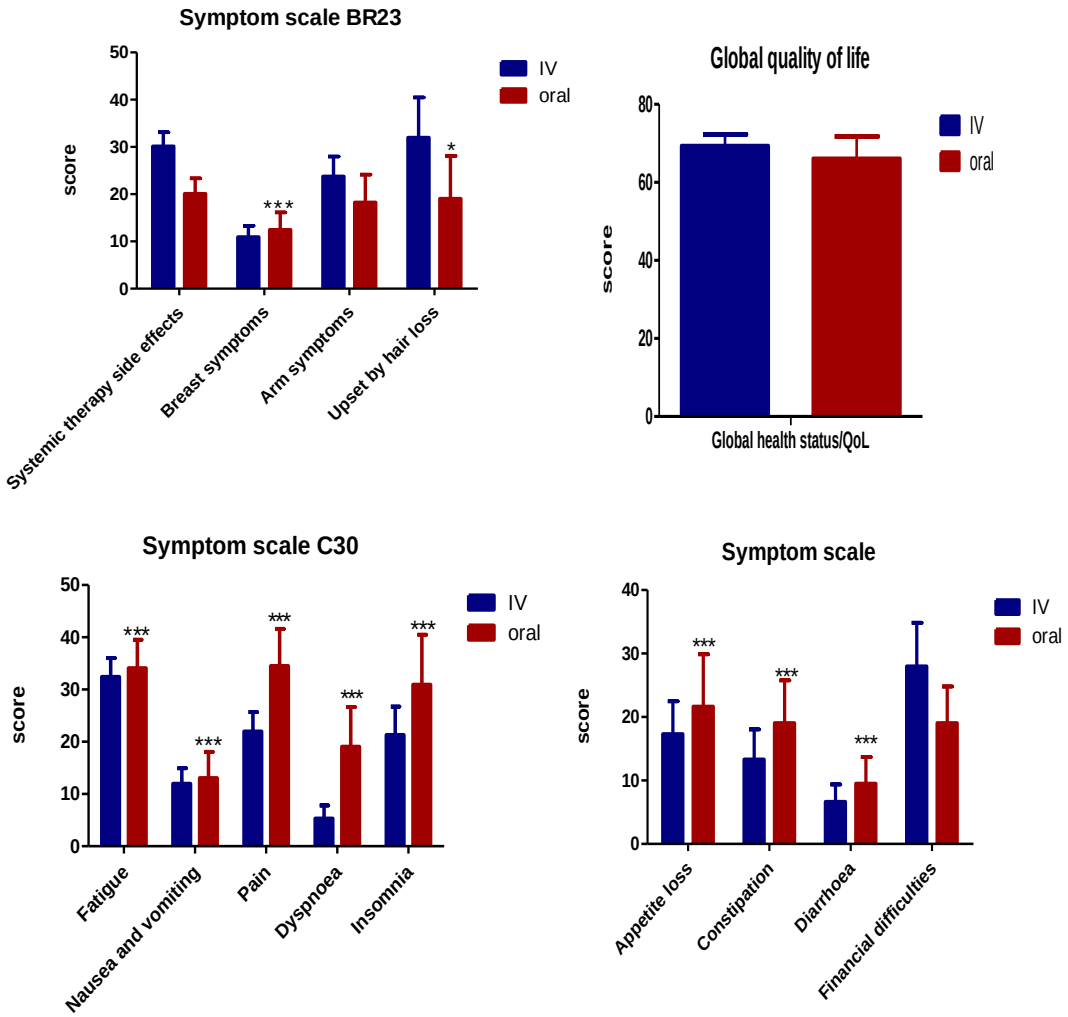




Comparison of data in different routes of administration

In different routes of administration, the sore for systemic therapy side effects for oral treatment was better than IV treatment. However, significant difference was not found. Except for arm symptom, financial difficulties, systemic therapy side effects score for other symptomology were significantly high in oral treatment. However the overall quality of life was good in both the treatment groups.

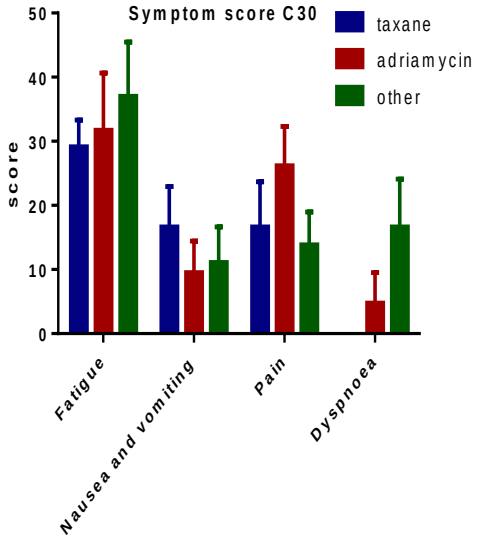
Figure 5.1.5. Symptom score and global quality of life for different routes of administration

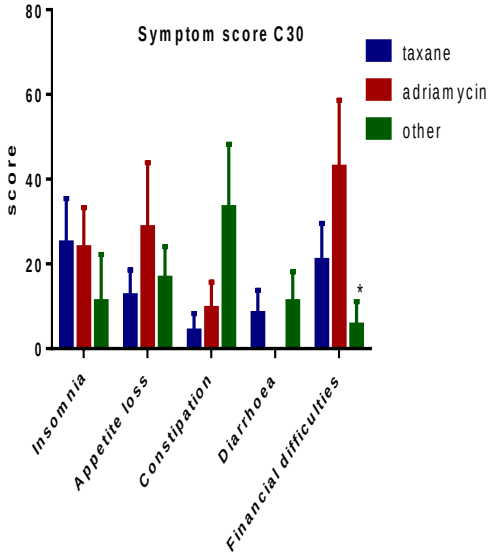


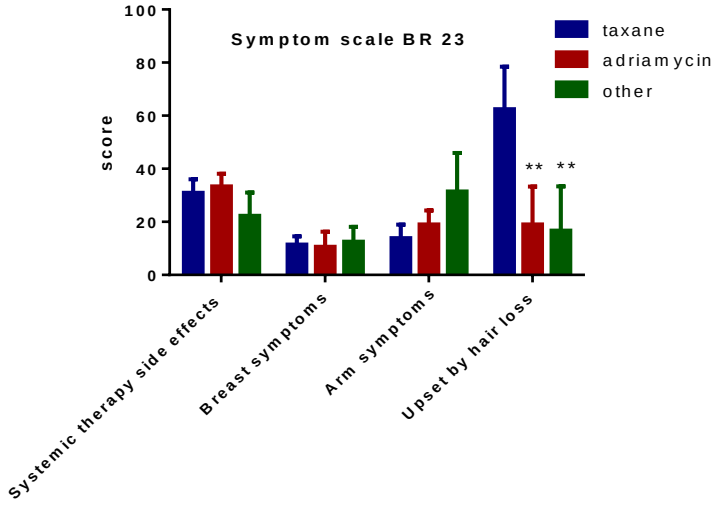
Comparison of data in different treatment group

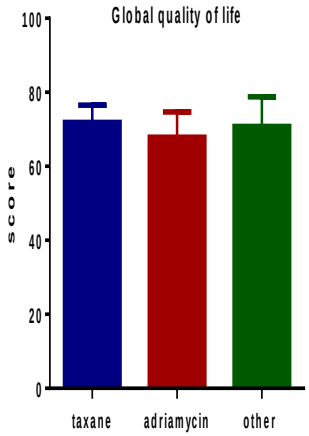
In the comparison of different treatment protocol for symptom score, side effects were less common while arm symptom were higher in other treatment group. Upset by hair loss symptom was significantly high in taxane based group as compared to other two groups. Overall on the basis of symptomology other treatment group was better. Financial difficulty score was high in Adriamycin treatment group. Overall quality of life was almost same in all the three group.

Figure 5.1.6. Symptom score and global quality of life of different treatment group









5.2. Metastatic lung cancer

5.2.1. Demographics

The metastatic lung cancer patients were divided into four groups same as metastatic breast cancer. The number of patients enrolled in each group is as follows.

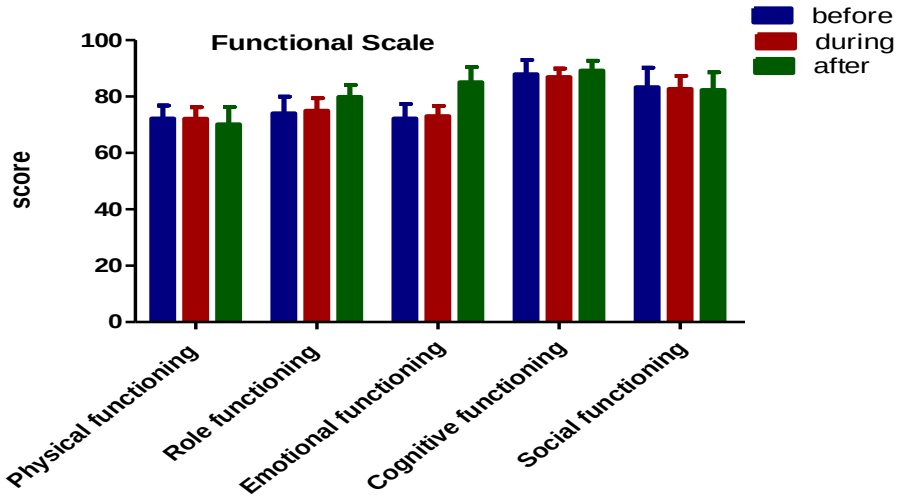
In the following table the basic characteristics of an individual group is presented. The mean age of all the patients was 59 years. Total individual number of patient enrolled in the study was 43. From which 33 were male and 9 were female.

5.2.2. Functional Score

Comparison of quality of life at different time interval

Different functional scores are listed in the table 5.2.3.. The scores are almost same in all the three groups for every function. No significant difference was found in any score.

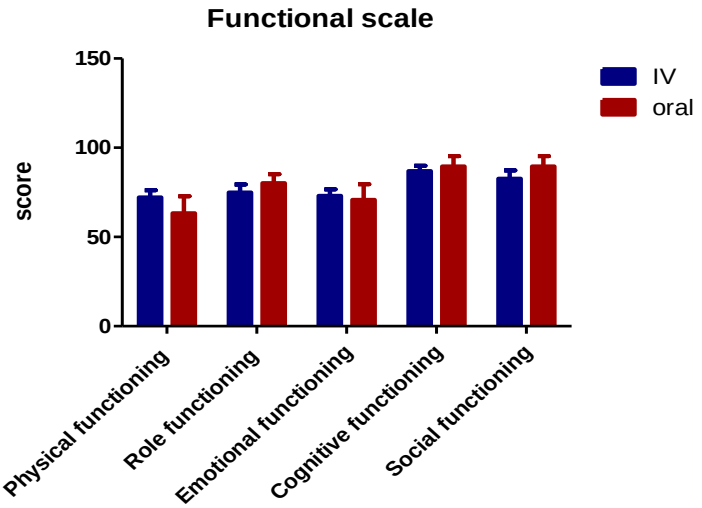
Figure 5.2.1. Functional score of patients at different time interval



Comparison of quality of life between different routes of administration

The functional score was almost similar in all the parameters. Though in role functioning, cognitive functioning and social functioning oral route of administration is better than the parenteral.

Figure 5.2.2. Functional score of patients for different routes of administration

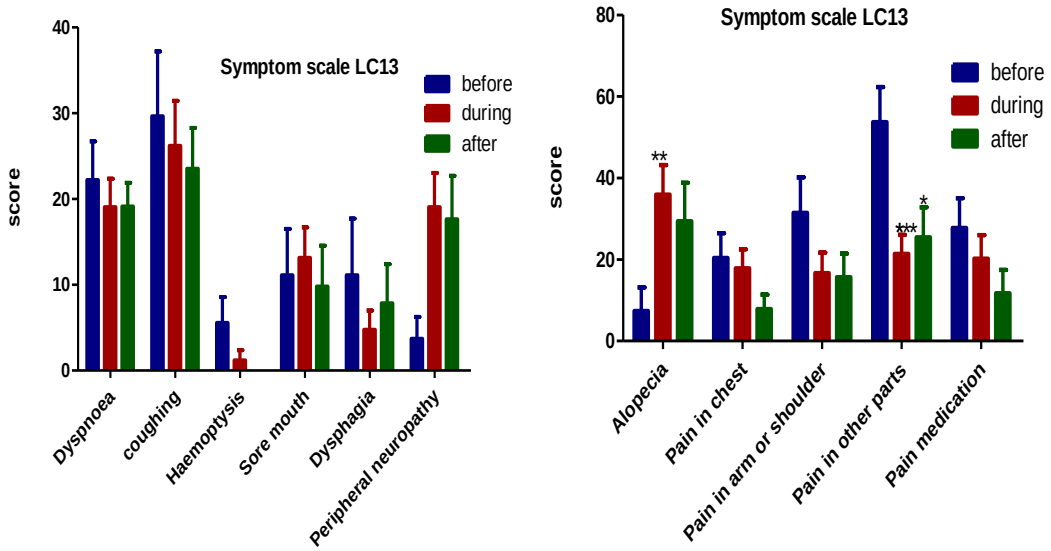


5.2.2. Symptom score

Comparison of quality of life at different time interval

The symptomology was found to be almost same in all the parameter except alopecia and pain in other parts. A significant difference was found in these two parameters. Pain in chest was high in before and during the treatment group which decreased in after the treatment group.

Figure 5.2.3.Symptom score of patients at different time interval

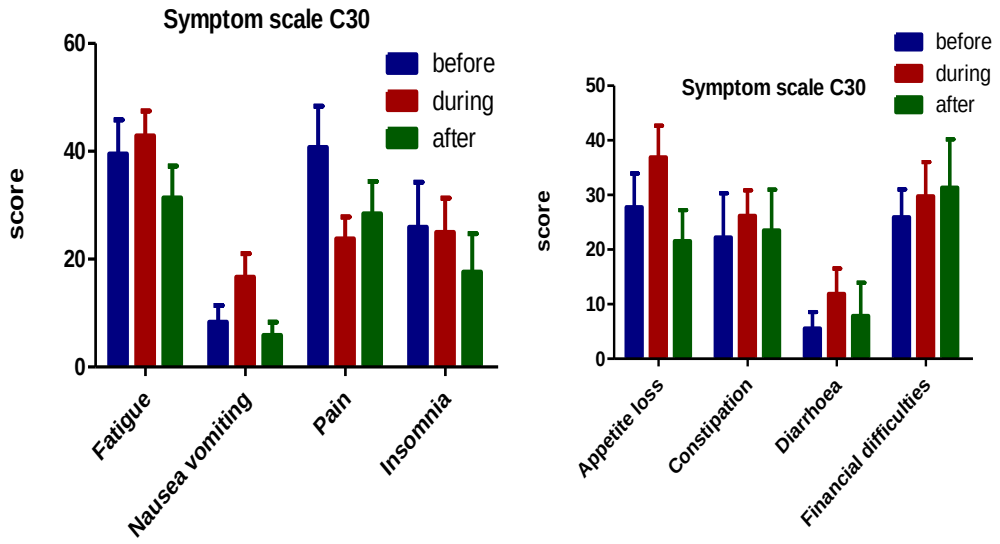


Comparison of quality of life between different routes of administration

In during the therapy group, fatigue, nausea and vomiting, appetite loss, constipation parameters were high as compared to the other two groups. We also observed that as

the time progresses, the financial difficulties increased but surprisingly insomnia got deceased. Though, significant difference was not observed. Financial difficulties were increasing as the time increases. Insomnia got decreased after the treatment.

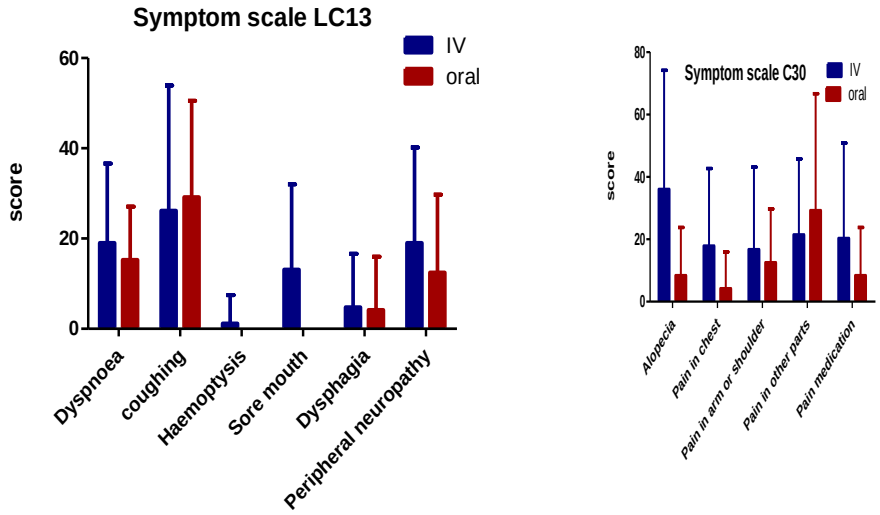
Figure 5.2.4. Symptom score of patients at different time interval



Comparison of symptom scorer between different routes of administration

Significant difference was not found in any parameter except pain in other parts of the body. Except coughing and pain in other parts, symptomology was higher in in IV treatment.

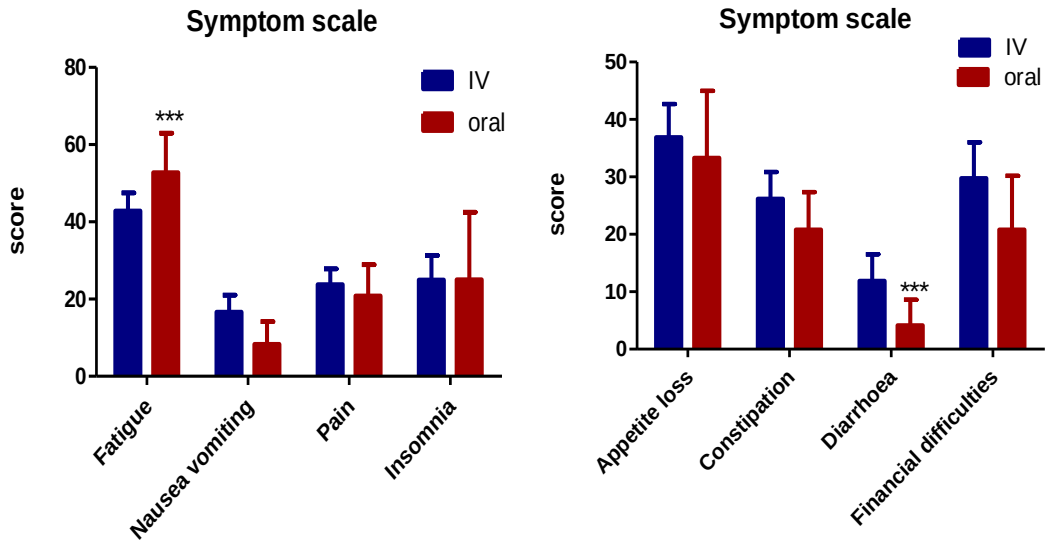
Figure 5.2.5. Symptom score of patients in different routes of administration



Symptomology of fatigue was significantly higher in oral patients as compared to IV. In diarrhoea score was significantly decreased in oral treatment and significant

difference was found. All other scores except for appetite loss were decreased in oral treatment.

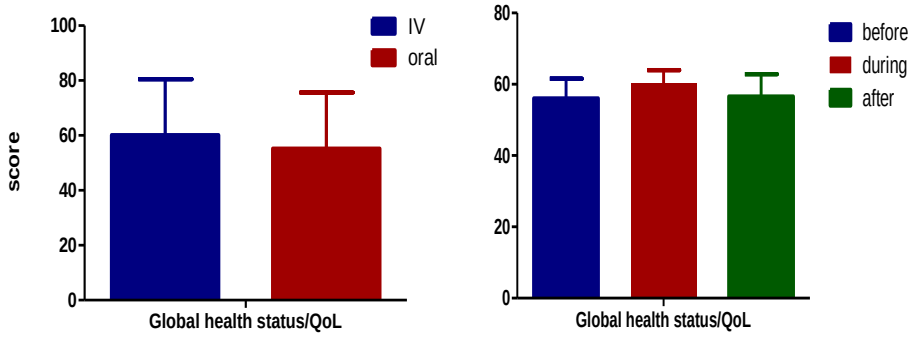
Figure 5.2.6. Symptom score of patients in different routes of administration



5.2.3.. Global Quality of life

The global quality of life was almost similar in all the three groups. During the treatment there was a slight increase in the score.. On IV vs. Oral also the score were same in all the groups

Figure 5.2.7 Global quality of life



5.3. Metastatic Colorectal Cancer

5.3.1. Demographics

In metastatic colorectal cancer, there are 3 groups, before, during and after the anticancer treatment. Numbers of patients enrolled in the study and their basic characteristics are listed in the following table.

5.3.2. Functional score and global health status

Here body image function score increases after the treatment, while anxiety and weight scores decreases after the treatment. For sexual interest and related questions, patients were not feeling comfortable to answer them. Overall the functional score was good in during the treatment patients. The global quality of life was good though slight increase in the score was noted in after the treatment group.

5.3.3. Symptom score

As seen in table 5.3.4. Before the anticancer treatment the symptomology was high which got decreased in during the treatment group. Though, significant difference was not found in any of the parameter.

6. Discussion

In our study, we measured the quality of life in Metastatic Breast Cancer, Metastatic Lung Cancer, and Metastatic Colorectal Cancer patients at different time interval i.e. before, during and after anticancer treatment. We also compared different routes of administrations i.e. Parenteral Vs. Oral. We also performed the quality of life assessment in different treatment protocol.

During the study, we screened 110 patients at Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad from these, 17 patients who refused to give written consent were not included in the study. Total 93 patients' were enrolled in the study and the data were analysed.

For the measurement of QoL, we used EORTC QLQ-C30 and core questionnaires for breast cancer (BR23), for lung cancer (LC13) and for colorectal cancer (CR29). C-30 represents the common cancer questions related to health and other factors. While, the core questionnaires contains the questions regarding factors that affects the specific cancer. We used BR23 for breast cancer, LC13 for lung cancer, CR29 for colorectal cancer along with C-30. These questionnaires contain three types of scores, Functional score, Symptom score and Global QoL score. Functional score represents how well one is functioning. Symptom score represents the symptomology that an individual has due to disease or any conditions. While global quality of life represents overall health status of an individual. Thus as the score increases, function and global

quality of life increases. While for the symptom score, as the score increases the symptomology increases.

6.1. Metastatic Breast Cancer

Total 50 patients were screened for metastatic breast cancer from which 8 patients refused to give written consent, thus 42 patients were enrolled in the study. While for the comparison of different routes of administration; 25 patients were enrolled in IV group and 14 patients were enrolled in oral group. For the comparison of different treatment protocol, total three groups were considered 1. Taxane based treatment protocol- the numbers of patients enrolled were eight, 2.Adriamycin based treatment protocol- The numbers of patients enrolled were seven and 3. Other treatment protocols – The numbers of patients enrolled were six. In other treatment group, gemcitabine, carboplatin, trastuzumab and vinorelbine were considered. The mean age was 51 years. The Body Surface Area got decreased in during the treatment group. We also observed that Random Blood Sugar increased at different time interval.

Functional score

The body image indicates one's perception for their body. In our study the function was high in before the therapy which got significantly decreases in other two groups. While for the different routes of administrations the score was significantly higher in oral treatment. For the comparison of different treatment, the function was higher in Adriamycin group was higher as compared to other two groups though, significant difference was not found.

For sexual enjoyment and sexual functioning, due to our culture of India patients were not feeling confortable to answer such questions.

For the future perspective, scores were almost similar at different time interval. While in comparison of IV vs. Oral, the score was significantly higher in oral patients. For different treatment protocol, the function was greater in Adriamycin and other treatment group as compared to taxane based treatment.

Physical functioning indicates the ability of an individual to perform physical tasks such as walking long distance, carrying heavy languages etc. Emotional functioning indicates how well one's mind set is? Physical functioning and emotional functioning were almost same at different time interval. While in IV vs. Oral comparison, in

physical functioning no significant difference was found but in emotional functioning a significant difference was found which suggests that the oral is better than IV. In different treatment comparison, the scores were almost same in all the three groups.

Role functioning indicates individual's role in performing their tasks. It was higher in before group as compared to during group, which again got significantly increased in after the treatment group. In IV vs. oral comparison also the score were significantly higher in oral treatment. In adriamycin group the score was insignificantly higher as compared to other treatment group.

Cognitive functioning indicates how well one can remember? And social functioning means social support. For both the functions, the scores were significantly higher in after the treatment group as compared to other two groups. Both of these functions were significantly higher in oral group. In cognitive functioning score was insignificantly higher in other treatment group as compared to taxane based treatment. While, social functioning was insignificantly higher in taxane group as compared to other groups.

Symptom score

At different time interval the symptoms of the systemic therapy side effects, breast symptom, arm symptom, upset by hair loss, fatigue, nausea, vomiting, pain, dyspnoea, insomnia, appetite loss, constipation, diarrhoea and financial difficulties were almost same. Financial difficulties were greater in during group as compared to other. While in the comparison of different routes of administration groups, overall symptomology were higher in oral group except systemic therapy side effect, arm symptom, upset by hair loss and financial difficulties. A significant reduction was seen in upset by hair loos symptom in oral group. In different treatment comparison also no difference was found in either of the symptom except upset by hair loss which was significantly higher in taxane group and financial difficulties which was significantly higher in Adriamycin group.

Global Quality of Life

The global quality of life i.e. overall health was good at different time interval. More even in different treatment protocol and in different routes of administration also, the overall health was good in all the groups. No significant difference was found in any comparison.

Our study results are concordance with a study carried out by Montazeri, et al (2008); they found that deteriorations in patients' scores for body image, sexual functioning and significant improvements for breast symptoms, systematic therapy side effects and patients' future perspective after chemotherapy. They also found significant change in function and global quality of life. So, considering that our results of global quality of life are in contrast with this result. [34]. Leng, et al. (2014) suggested that women with breast cancer had good quality of life and had significant concern over the financial impact [35], Our results for global quality of life were consistent with this study.

Our study suggests taxane based treatment have lower functional problem and in symptom scale the scores were higher for upset by hair loss, nausea and vomiting, insomnia. This results are consistent with a study done by Hall et al (2014) reported poor quality of life for taxane based treatment protocols. [49]. A state-wide population based cohort study done in Germany by A. Waldmann et al (2007) for the measurement of quality of life in breast cancer showed that the overall quality of life was high in female though the patients were more concerned about their financial difficulties. [37] Which is consistent with our study results.

Myung Kyung Lee et al (2007) found that the patients who didn't complete of treatment were having poorer quality of life as compared to the patients who completed the therapy. The post treatment group showed very poor score for role functioning, cognitive functioning and social functioning. For the symptom score the patients were also concerned about fatigue and financial difficulties. They also found that the higher score of overall quality of life was related to the satisfactory medical care, completion of treatment, being involved in decision making process and overall good health before surgery. [38]

Changes in Functional and symptom scores were observed in before, during and after the treatment group this findings are consistent with the findings of Montazeri, et al (2000) suggested that functional and symptoms scales changes over time, as a function of a patients' performance status changes.[36]

6.2. Metastatic Lung Cancer

In this cancer total 49 patients were screened, from which 6 patients refused to give written consent. Thus total 43 patients were enrolled in the study from which 33 were

male and 9were female. 18, 28,17 patients were enrolled in before during and after anticancer treatment group respectively and in oral group 8 patients were enrolled. We performed 2 types of comparison in this cancer, first one between different routes of administration and second one between different time intervals. The mean age of the patients was 59 years.

Functional score

There are five functional scores. All of the functions i.e. Physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning, were found to be almost equal at different time intervals. Slight improvements in scores were noted in after the treatment group.in comparison of IV vs. Oral. Physical functioning was better in IV as compared to oral. In remaining functions scores of both the groups were almost equal.

Symptom score

Dyspnoea and coughing, both were decreasing as the time increases, but no significant difference was found. While in IV vs. Oral, dyspnoea was decreasing in oral group as compared to IV, while the coughing was increasing. Haemoptysis was decreasing in during and after anticancer treatment, in after group the score was 0 representing none of the patient was having this symptom. In oral group also the score was found to be 0 as compared to IV. Sore mouth and dysphagia were significantly decreasing in during group but in after group dysphagia got increased. In oral group sore mouth was not observed in any patient and dysphagia was almost same in both the group.

Peripheral neuropathy and alopecia, they both got increased in during group and after group it got decreased. But in alopecia only, significant difference was noted. In oral group the score was significantly less as compared to the IV group

Symptom of pain in chest and pain in arm and shoulder were decreasing throughout the study. Evan in oral group also the score for above mentioned symptom were less as compared to the IV group but significance was not observed in any group. Pain in other part of the body was high in before, which got significantly decreased in during group and again increased in after group. In oral group the score was high as compared to IV. Need of pain medication decreases throughout the study even in oral group also the need is less as compared to IV.

Fatigue and nausea vomiting were insignificantly higher in during group as compared to other two groups. While in oral group symptom of fatigue got significantly increased as compared to IV. For nausea vomiting, the score decreased.

Insomnia was decreasing throughout the study but pain score increased after the treatment as compared to during the treatment. While in oral group insomnia got increased and pain score decreased as compared to IV group.

Symptom of diarrhoea and financial difficulties were higher in during the treatment group as compared to other two groups. While in oral group both the symptoms were low as compared to IV group. In oral group significant difference was noted for diarrhoea.

Global quality of life

The global quality of life that is over all health was almost equal throughout the study; even in IV vs. Oral comparison also score were found to be almost same. No significant difference was noted in any group.

Wintner (2013) measured the quality of life during chemotherapy in lung cancer patients the study that irrespective of chemotherapy all the patients showed stable quality of life. Patients receiving 3rd line or above palliative treatment had worn QOL while patients receiving 1st line treatment had better QoL as compared to above.[43] which is consistent with our study results.

B. Bergman, et al (1994) showed that all item scores changed significantly i.e. treatment toxicities increased and lung cancer symptoms decreased.[39]

6.3. Metastatic Colorectal Cancer

Total 11 patients were screened for metastatic colorectal cancer from which 3 patients refused to give written consent. Thus total 8 patients were enrolled in the study. From these 8 patients, 6 were male and 2 were female. In patient distribution, 5 were in before the treatment group, 2 were in during the treatment group and 3 were in after the treatment group. The mean age of the patients was 57 years.

Functional score

A slight decrease in body image function was noted in during the treatment as compared to before the treatment, which increased after the treatment. Anxiety was observed to be decreasing throughout the study. Weight gain was observed in during

treatment which decreases after the treatment. For sexual interest, patients were not feeling confortable to answer the questions thus the scores are missing.

Our results shows that the physical functioning, role functioning, cognitive functioning, social functioning and emotional functioning were improved in during the treatment as compared to before the treatment. After the treatment score were decreasing.

Symptom score

Urinary incontinence was not observed in during and after the treatment groups. Urinary frequency was high before the treatment group which decreases during the treatment. Stool frequency was greater in during group as compared to before the treatment which got decreased in after the treatment.

Abdominal pain, dry mouth, buttock pain, bloating and hair loss were increased in during the treatment group as compared to before the treatment group, from which symptom of bloating and dry mouth got increased after the treatment group. Hair loss and buttock pain were not observed in after the treatment. Symptom of taste decreased throughout the study. While flatulence increased during the treatment as compared to before and after the treatment.

Symptom of faecal incontinence, sore skin, stoma care problem and nausea vomiting were not observed during and after the treatment. Embarrassment was decreased during the treatment and after the treatment it increased. For impotence and dyspareunia, patients were not feeling confortable to answer the questions, thus the scores are missing.

Scores for pain and dyspnoea, were high in during the treatment group as compared to other two groups. While, insomnia was decreasing in after the treatment group. Appetite loss was decreasing throughout the study. Constipation increased during the treatment, while diarrhoea was not observed during the treatment. Financial difficulties were less during the treatment as compared to before and after the treatment. None of the function shows significant difference.

Global quality of life

The overall health was same in all the three groups but a slight increase was seen in after the treatment group was seen. Sample size was small to analyse,

Study carried out on advanced colorectal patient by Urdaniz, et al (2006) suggests that patients receiving treatment had higher score for functional capacity and low scores for toxicity, these results are consistent with our study. [44]

In a study carried out by Bang et al (2005) for the palliative treatment suggests decreased symptoms such as pain and sleep disturbance. Significant improvement was noted in functional score but the effect did not persist throughout the course. The anxiety scores decreased throughout the period of intervention [43], these data are consistent with our study results.

6.4. Limitation

Small sample size, single centric study and short duration of our study are the limitation of our study.

Further multicentric study with large population and longer duration are warranted to investigate the outcome and meaningful data with respect to quality of life

Conclusion

Overall, the quality of life was better in during the therapy group of all the three cancer. The scores for symptom and functional scales were changing throughout the study. We also found that the functional scale was better in oral group for all the cancers. However, the symptom scale was high in metastatic breast cancer and was decreasing in metastatic lung cancer.

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"CORRELATION BETWEEN IMPROVEMENT IN OVERALL SURVIVAL (OS) AND EVENT FREE SURVIVAL (EFS) IN DIFFERENT TREATMENT PROTOCOL (BFM-90, MCP-841) AMONG PATIENTS WITH ACUTE LYMPHOBLASTIC LEUKAEMIA (ALL)"

A Thesis Submitted to

NIRMA UNIVERSITY

In Partial Fulfillment for the Award of the Degree of

MASTER OF PHARMACY

IN

CLINICAL PHARMACY

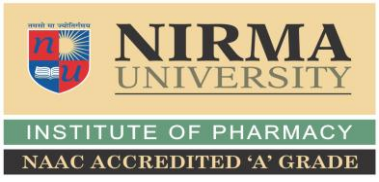
BY

Ms. JHIL N. KADAKIA (14MPH701), B. PHARM.

Under the guidance of

Prof. JIGNA S. SHAH – GUIDE
Professor and Head, Department of Pharmacology

Dr. DEEPA H. TRIVEDI- HOSPITAL GUIDE
M.D. (USA), Hemato-Oncologist,
Hemato-Oncology Clinic, Vedanta institute of medical science, Ahmedabad.



Department of Pharmacology
Institute of Pharmacy
Nirma University
Ahmedabad-382481
Gujarat, India.

May 2016

CERTIFICATE

This is to certify that the dissertation work entitled "Correlation between improvement in overall survival (OS) and event free survival (EFS) in different treatment protocol (BFM-90, MCP-841) among patients with acute lymphoblastic leukaemia (ALL)" submitted by Ms. Jhil Kadakia (14MPH701) 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 Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad, 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.

Hospital Guide

Dr. Deepa H. Trivedi
M.D. (USA),
Pediatric Hemato-oncologist,
Hemato-Oncology Clinic,
Vedanta institute of medical science,
Ahmedabad

Academic Guide:

Prof. Jigna S. Shah
M. Pharm., Ph.D.,
Professor and Head,
Department of Pharmacology,
Institute of Pharmacy,
Nirma University

Prof. Manjunath Ghate
M. Pharm., Ph.D.
Director,
Institute of Pharmacy,
Nirma University

Date: 2nd May, 2016

DECLARATION

I hereby declare that the dissertation entitled "Correlation between improvement in overall survival (OS) and event free survival (EFS) in different treatment protocol (BFM-90, MCP-841) among patients with acute lymphoblastic leukaemia (ALL)", 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 Dr. Deepa Trivedi, Pediatric Hemato-Oncologist, Hemato-Oncology Clinic, Vedanta Institute of Medical Science, Ahmedabad,. 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.

Ms. Jhil Kadakia (14MPH701)
Department of Pharmacology,
Institute of Pharmacy,
Nirma University,
Sarkhej - Gandhinagar Highway,
Ahmedabad-382481,
Gujarat, India

Date: May, 2016

Introduction

Cancer is a leading cause of morbidity and mortality. Worldwide 13 % of all deaths are cancer related among these 70% of deaths belong to low and middle income countries.(1) In children total number of new cases have crossed 200,000 worldwide and 80% of them are reported from developing world. (2) In developed countries or resource rich countries seven out of ten cancer children gets cured with five years overall survival of more than 95% in certain cancer such as Hodgkin's disease and retinoblastoma. (3,4) Leukemia is one of the foremost prevalent childhood cancers in India with varied magnitude between 25 to 40%. Among all reported leukemia cases; acute lymphoblastic leukemia occupies 60-85%. (5–8)

ALL is a heterogeneous disease both in terms of its pathology and the populations that it affects (9,10). Clinical presentation of ALL consists of fatigue, fever, loss of appetite or weight, night sweats, severe unusual bone and joint pain, hepatomegaly, splenomegaly, lymphadenopathy, petechiae, purpura or ecchymosis. Disease related symptoms also include pallor, tachycardia and a flow murmur. (11)

The prognosis of ALL in the underprivileged world remains low due to multiplicity of clinical and social factors. Cure rates of all cancers especially leukemia in underprivileged countries is law due to multiple factors, these includes lack of resources available to both patients and health care professionals. Thus, to enhance patient's survival rate in underprivileged countries, it is necessary to initiate research in this field. With latest combination chemotherapy protocols, 5 year overall survival rate in children is about 80% (12)

As per some publications from India T-cell immunophenotype is more prevalent. T-cell phenotype carries a poorer prognosis than process B-cell phenotype. (5–8) Previously T-cell phenotype was related to ALL in economically deprived area and more in malnourished populations. However, prevalence of pre B type is more common in newer studies. (13). In the 1980s the EFS of ALL has constantly improved (14–16) From the developed world , childhood ALL the overall 5-year EFS is around 80 % and the 10-year EFS is around 60% (14). Probable 5 and 10 year OS rates for patients diagnosed between 2000 to 2004 were 88 and 84%, respectively (15). For youngsters and for those who were diagnosed between the years 2005 to 2009, the 10-year survival rate is estimated to be 88 % In contrast, within the underprivileged

world, recovery rates are below 35 % (17,18), partially due to negligence of the treatment(19) and/or shortage of purposeful, multidisciplinary pediatric oncology units (20). When the pediatric populations of the underprivileged world are treated by international treatment protocols, EFS and OS at the end of 5 years are enhanced. Still treatment related mortality remains high as compared to developed world. (21). Treatment Strategies in ALL involves combination of chemotherapy, radiotherapy and bone marrow transplantation. (22)

The success of combination chemotherapy of ALL depends on various drugs and constant refinement in therapy for example substitution or use of high dose methotrexate instead of cranial radiation has led to reduction in CNS relapse and reduction in long term neurological side effects(23–25). In the treatment of childhood ALL much progress has been made since last 30 years with reformed risk assessment and treatment and better supportive care. 80–95% of newly diagnosed children with standard risk can be cured (26,27). Despite these success around 20% of the total children with ALL will relapse.(28)

Treatment of ALL in pediatric population is successful most of the time. However, high dose of chemotherapy may be associated with sever treatment related adverse effects. Hence research is going on to optimize drug schedule and duration of treatment. (29) Relapse still accounts for major cause of morbidity and mortality in children with ALL. (30)

Outcome of treatment depends on age, immunophenotype, cytogenetics (molecular profiles) of the patients due to t (4:11) (MLL gene) and poorer tolerance to chemotherapy. (31). In recent trials it is concluded that the children between 1 to 10 year of age has improved prognosis with higher rate of 5 year EFS of 85%.(32) Older children (age >10 years), adolescents, adults however still have a poorer t (9; 22) or Philadelphia chromosome increases as the age increases. As the age increases specially in older individuals, the chances of having other comorbid conditions (hypertension, diabetes mellitus, renal and liver dysfunction, etc.) increases which have possibility to limit the administration of intensive treatment. Many oncologists have noted higher grade of toxicity in older patient as compared to younger patients when vincristine and l-asparaginase were administered. Because of the above reason adult ALL protocol contains lower dose of intermittent treatment with

myelosuppresive drugs. However pediatric treatment protocol contains continuous chemotherapy with intensive vincristine, l-asparaginase and steroids.(22)

Keeping these insights, we designed a single centric retrospective study to measure EFS and OS with respect to clinical features and to correlate clinical features with EFS and overall survival of the two treatment protocols, specifically BFM-90 and MCP-841.

Literature Review:

Borkhardt et al (1997) analyzed 334 unselected cases of paediatric ALL patients consecutively referred over a period of 5 and 9 months, respectively. The overall incidence of the t(12;21) in paediatric ALL is 18.9%. In pediatric acute lymphoblastic leukemia (ALL), the most common translocations, t(9;22) and t(4;11), have been associated with a poorer clinical outcome. By conventional cytogenetics, however, this chromosomal abnormality is barely detectable and occurs in less than 0.05% of childhood ALL. Based on this prospective analysis, A total of 342 children were retrospectively investigated for the presence of TEL/AML1 fusion gene and 99 cases (28.9%) were positive. The patients expressing the TEL/AML1 fusion mRNA appeared to have a better event-free survival (EFS) than the patients who lacked this chimeric product. Whereas three of the TEL/AML1 positive cases (3.0%) have relapsed to date, 27 patients without TEL/AML1 rearrangement (11.1%) suffered from relapse. To date, the only subset of B-lineage ALL with a favorable prognosis has been the hyperdiploid group (DNA index ≥1.16 .1.6). These findings reinforce the need to include the molecular screening of the t(12;21) translocation within ongoing prospective ALL trials to prove definitively its prognostic impact.[(8)]

Kantarjian et al (2000) carried out a study involving adults with newly diagnosed ALL referred since 1992 were entered onto the study; treatment was initiated in 204 patients between 1992 and January 1998. No exclusions were made because of older age, poor performance status, organ dysfunction, or active infection. Median age was 39.5 years; 37% were at least 50 years old. Mature B-cell disease (Burkitt type) was present in 9%, T-cell disease in 17%. Leukocytosis of more than 30 3 109/L was found in 26%, Philadelphia chromosome–positive disease in 16% (20% of patients with assessable metaphases), CNS leukemia at the time of diagnosis in 7%, and a

mediastinal mass in 7%. Treatment consisted of four cycles of Hyper-CVAD alternating with four cycles of high-dose methotrexate (MTX) and cytarabine therapy, together with intrathecal CNS prophylaxis and supportive care with antibiotic prophylaxis and granulocyte colony-stimulating factor therapy. Maintenance in patients with nonmature B-cell ALL included 2 years of treatment with mercaptopurine, MTX, vincristine, and prednisone (POMP). Overall, 185 patients (91%) achieved complete remission (CR) and 12 (6%) died during induction therapy. Estimated 5-year survival and 5-year CR rates were 39% and 38%, respectively. The incidence of CNS relapse was low (4%). Compared with 222 patients treated with vincristine, doxorubicin, and dexamethasone (VAD) regimens, our patients had a better CR rate (91% v 75%, P < .01) and CR rate after one course (74% v 55%, P < .01) and better survival (P < .01), and a smaller percentage had more than 5% day 14 blasts (34% v 48%, P 5 .01). Previous prognostic models remained predictive for outcome with Hyper-CVAD therapy.[9]

A retrospective cohort of participants of the Childhood Cancer Survivor Study was used to compare 1,765 adult survivors of childhood ALL to 2,565 adult siblings of childhood cancer survivors by **Oeffinger et al (2003).** Body-mass index (BMI; kilograms per square meter), calculated from self-reported heights and weights, was used to determine the prevalence of being overweight (BMI, 25-29.9) or obese (BMI >30.0). Polytomous logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for being overweight or obese among ALL survivors relative to the sibling control group.The age- and race-adjusted or for being obese in survivors treated with cranial radiation doses >20 Gy in comparison with siblings was 2.59 for females (95% CI, 1.88 to 3.55; P < .001) and 1.86 for males (95% CI, 1.33 to 2.57; P < .001). The OR for obesity was greatest among females diagnosed at 0 to 4 years of age and treated with radiation doses >20 Gy (OR, 3.81; 95% CI, 2.34 to 5.99; P < .001). Obesity was not associated with treatment consisting of chemotherapy only or with cranial radiation doses of 10 to 19 Gy. Cranial radiotherapy >20 Gy is associated with an increased prevalence of obesity, especially in females treated at a young age. It is imperative that healthcare professionals recognize this risk and develop strategies to enhance weight control and encourage longitudinal follow-up.[16]

Xavier et al (2004) analyzed the benefits of a risk-adapted postremission strategy in adult lymphoblastic leukemia (ALL), and re-evaluated stem-cell transplantation (SCT) for high-risk ALL. A total of 922 adult patients entered onto the trial according to risk groups: standard-risk ALL (group 1), high-risk ALL (group 2), Philadelphia chromosome-positive ALL (group 3), and CNS-positive ALL (group 4). All received a standard four-drug/4-week induction course. Patients from group 1 who achieved a complete remission (CR) after one course of induction therapy were randomly assigned between intensive and less intensive postremission chemotherapy, whereas those who achieved CR after salvage therapy were then included in group 2. Patients in groups 2, 3, and 4 with an HLA-identical sibling were assigned to allogeneic SCT. In groups 3 and 4, autologous SCT was offered to all other patients, whereas in group 2 they were randomly assigned between chemotherapy and autologous SCT. Overall, 771 patients achieved CR (84%). Median disease-free survival (DFS) was 17.5 months, with 3-year DFS at 37%. In group 1, the 3-year DFS rate was 41%, with no difference between arms of postremission randomization. In groups 2 and 4, the 3-year DFS rates were 38% and 44%, respectively. In group 2, autologous SCT and chemotherapy resulted in comparable median DFS. Patients with an HLA-matched sibling (groups 2 and 4) had improved DFS. Three-year DFS was 24% in group 3. Allogeneic SCT improved DFS in high-risk ALL in the first CR. Autologous SCT did not confer a significant benefit over chemotherapy for high-risk ALL.[(10)]

Christine et al (1977) reported that nine younger children (mean age 6 * 3 years) and 6 older children (mean age 9 *0 years), previously treated for acute lymphoblastic leukaemia by cranial irradiation and subsequently by 2 or 3 years of chemotherapy, were assessed in terms of intellectual development in relation to 15 controls, matched individually for age, sex, and social background. All children were functioning within a normal range. The older group of children performed as well as their matched controls in all tasks. However, the younger group tended to perform somewhat below their matched controls, and this applied especially to tasks measuring quantitative, memory, and motor skills, but not to language tasks. It is concluded that there is a

continual need to monitor the development of children treated for leukaemia, especially when diagnosed in the 2- to 5-year age range.[17]

Gökbuget et al (2012) reported that despite improvements in first-line therapies, published results on the treatment of relapsed adult acute lymphoblastic leukemia (ALL) show that prognosis is still poor. A total of 547 patients with a median age of 33 years (range, 15-55) experiencing their first relapse (406 vs 141 shorter or longer than 18 months from diagnosis) were evaluated. The aim of salvage therapy was to achieve a complete remission (CR) with subsequent stem cell transplantation (SCT). The CR rate (assessed in Philadelphia chromosome and BCR-ABL–negative ALL without CNS involvement) after the first salvage in relapse after chemotherapy (n =224) was 42%. After failure of first salvage (n = 82), the CR rate after second salvage was 33%. In relapse after SCT (n = 48) the CR rate after first salvage was 23%. The median overall survival after relapse was 8.4 months and survival was 24% at 3 years. Prognostic factors for survival were relapse localization, response to salvage, performance of SCT, and age. Overall survival appeared superior compared with previously published studies, likely because of the high rate of SCT in the present study (75%). [18]

Willemze et al (1975) reported that during the period from January 1970 until December 1973, therapy was started in 41 previously untreated adolescents and adults with acute lymphoblastic leukemia. Induction therapy was started with vincristine and prednisone in all patients, resulting in complete remission in 19 and death due to infection during the first month in one case. The overall remission rate was 83%. Significantly higher initial leukocyte counts were found in the group treated with vincristine, prednisone, and daunorubicin. Meningeal leukemia prophylaxis, by either periodic methotrexate injections given intrathecally or a combination of cranial irradiation and intrathecally administrated methotrexate, was administered in 29 therapy responders. The median duration of complete remission obtained with various maintenance therapy schemes was 13 months. A second remission was obtained in 17 cases (77%). The percentage and duration of remission and the survival time in our

group of adolescents and adults were comparable to those currently being achieved in other centers, but not as good as those reported for children treated with the same protocols.[19]

Baccarani et al (1982) reported that the case histories of 293 adolescent and adult patients with acute Iymphoblastic leukemia (ALL) first seen and treated between 1969 and 1979 are reviewed. A complete remission (CR) was achieved in 79% of cases. Male sex, advanced age (a30 yr old). and early CNS involvement were the major determinants of remission failure. Median duration of first CR was 1 6 mo. with 23 patients (actuarial proportion 25%) alive and relapse-free at 5 yr. The major determinant of first CR length was white blood cell (WBC) count (best cut-off value at 35 x 109/liter). Maintenance chemotherapy was apparently more effective when 4 or more than 4 drugs were employed. "Low risk" patients (WBC count <35 x 109/Iiter still relapsed rather frequently (32% at 1 yr. 49% at 2 yr), with 33% of them alive and relapse-free at 5 yr. "High risk" patients (WBC count ı35 x 109/Iiter± early CNS involvement ± morphological L3 subtype ± B-cell leukemia) relapsed very quickly (50% at 6 mo, 70% at 1 yr), with only 6% of them relapse-free at 5 yr.[13]

Schrappe et al (2000) designed a trial ALL-BFM 90 to improve outcome in patients with childhood acute lymphoblastic leukemia (ALL) by using a reduced treatment regimen. Patients were stratified into a standard risk group (SRG), a medium-risk group (MRG), both defined by adequate early treatment response; and a high-risk group (HRG), defined by inadequate response to the cytoreductive prednisone prephase, induction failure, or Philadelphiachromosome positive ALL. Four treatment modifications were evaluated: dose intensification in induction by a more rapid drug sequence; administration of L-asparaginase during consolidation therapy in the MRG (randomized); enforced consolidation by rotational elements in the HRG; and reduction in the dose of anthracyclines and use of only 12-Gy preventive cranial radiotherapy in the MRG and HRG, with the aim of avoiding toxicity. Among all 2178 patients (I 18 years of age), the 6-year event-free survival (EFS) rate (6 SE) was 78% 6 1%, with a median observation time of 4.8 years. EFS was 85% 6 2% in the SRG (n 5 636) and 82% 6 1% in the MRG (n 5 1299). L-asparaginase did not improve outcome in the MRG: the event-free interval was 83% 6 2% with L-asparaginase (n 5

528) and 81% 6 2% without it (n 5 557). Because there were more systemic relapses in the HRG (n 5 243), EFS was 34% 6 3%, an outcome inferior to that in the HRG in a previous trial, ALL-BFM 86, in which EFS was 47% 6 5% (P 5 .04). The rates of isolated central nervous system relapse in the MRG and HRG were 0.8% and 1.6%, respectively; thus, the 12-Gy preventive cranial radiotherapy regimen apparently provided sufficient central nervous system prophylaxis. The overall improvement over the results in ALLBFM 86 (6-year EFS, 72%; P 5 .001) was based on fewer recurrences among patients in the MRG with B-cell-precursor ALL, indicating an advantage of more condensed induction therapy. [20]

Aim and Objective

In general, the prognosis of childhood ALL in the developing world remains poor due to a multitude of adverse clinical and social factors, the most prominent among these being the lack of resources available to both patients and health care professionals. Thus, in order to improve the survival of patients with ALL in developing countries, it is important to conduct research into the biology, response to treatment and prognostic factors in the developing countries themselves. Keeping these insights, we designed a single centric retrospective study with the following aim and objective:

- To investigate the epidemiological, clinical, prognostic features and treatment characteristics in patients with acute lymphoblastic leukemia.
- To determine event free survival and overall survival.
- To correlate immunophenotyping with overall survival and event free survival.
- To determine cost effectiveness of the two treatment protocol (BFM-90 protocol and MCP-841).

Study Protocol

3.1 Study Design:

A single centric retrospective study at Hemato Oncology Clinic Vedanta Institute of Medical Science, Ahmedabad from December 2012 to April 2013.

3.2 Study Population:

Both male and female of the all ages diagnosed with ALL were included in the study.

3.3 Inclusion Criteria:

- Patients diagnosed with Acute Lymphoblastic Leukemia.
- Minimum 2 months follow up.
- clinical laboratory results while Patients' Screening are within clinically acceptable range
- Patients with cytogenetics and flow cytometry reports.
- Patients treated with BFM-90 or MCP-841.
- Diabetes and hypertension patients included.

3.4 Exclusion Criteria:

- Less than 2 months follow up
- Leukemic children with concomitant chronic diseases, subjects without complete remission of the disease (day 30 of the induction protocol), hepatic failure, severe septicemia, and adolescents with oral contraceptives or nicotine abuse were excluded from the study.

3.5 Study Methodology

The study included 142 patients, first seen between 2006 and 2012 at the Hemato Oncology Clinic Vedanta Institute of Medical Science, Ahmedabad. The diagnosis of ALL was based on examination of Bone marrow aspiration and biopsy. Patients were analyzed for Hb concentration, platelet count, WBC count, sex, age, mediastinum involvement, lymphadenomegaly, spleenomegaly, hepatomegaly, proportion of blast cells in the marrow. Patients were treated as per BFM-90 or MCP-841 as per Principle Investigator discretion. Information on treatment like drug name, dose, and schedule

of the agents that are employed for Induction, Consolidation and Reinduction chemotherapy were collected. From the data sheet OS and EFS were also analyzed.

3.6 Outcome measures:

- WBC count
- Hemoglobin level
- Platelet count
- SGPT (ALT) level
- Immunophenotyping
- Complete Remission: A complete remission (CR) was defined as less than 5% blasts in a normocellular marrow aspirate and the absence of clinical evidence of disease.
- Overall survival: OS was calculated from the date of commencement of treatment to the date of last follow-up.
- Event free survival: EFS was calculated from the date of commencement of treatment to the date of last follow up or an event

3.7 Ethical Consideration:

The study protocol was approved by Ethics Committee of CIMS, Ahmedabad. (Approval No. O-501/2012)

3.8 Statistical analysis:

Descriptive clinical data were expressed in percentage.. Kaplan Meier curve was generated.

Patients suffering with ALL were treated with the standard treatment protocol, BFM-90 or MCP-841. Clinical and biological features of all patients such as sex, CBC (complete blood count) SGPT and immunophenotype in context of EFS and OS is presented in Table I. Details of chemotherapy protocols are summarized in Table IIa and IIb respectively. During the study we screened 142 patients, from which 27 patients were lost to follow up and/or had insufficient data. So they were not included in the study. Total 115 patients' data first seen between 2008 and 2012 at the Hemato-

Oncology Clinic, Vedanta Institute of Medical Sciences, Ahmedabad were analyzed. From these, 2 patients had induction death, 2 had infection death and 2 patients did not achieve complete remission (CR) and 30 patients had relapse and died.

TABLE I: CHARACTERISTICS OF PATIENTS SUFFERING FROM ACUTE LYMPHOBLASTIC LEUKEMIA

Characteristic	**BFM-90**	**MCP-841**	**Total**	**Per cent**
Number of patients	77 (66.95)	38 (33.04)	115	
Age (years)				
<1	0	0	0	0
1-18	58	14	73	63.47
>18	19	23	42	36.52
Sex				
Male	57	25	83	72.17
Female	20	12	32	27.8
Hemoglobin (g/dl)				
<or =10	49	22	72	62.60
>10	28	15	43	37.39
WBC counts (per cmm)				
<20,000	57	25	83	72.17
20,000-100,000	18	05	23	20
>100,000	02	07	09	7.82
Platelet count($\times 10^3$/cmm)				
<150	47	22	70	60.8
150-450	28	14	42	36.52
>450	03	01	4	3.47
SGPT (UL)				
<5	0	0	0	0
5-40	45	21	67	58.2

>40	32	16	48	41.7
Immunophenotype				
B-cell (50)	37	13	50	86.20
T-cell (8)	5	3	8	13.79

From 115 patients, 83 were male and 32 were female. The incidence of childhood (1 to 18 years) ALL was found to be 73 (63.47%). 42 (36.52%) patients had age greater than 18 years; from which 17 (14.78%) patients were above 40 years of age. Our results are consistent with Advani et al (1999) findings that the incidence of ALL in childhood patients is found to be 57.2%. Some other reports from Germany, Austria and Switzerland have shown that the incidence of ALL was 61.3% in the 2-9 years age group(33,34)

Our study showed that most of the patients (62.60%) were having low hemoglobin levels (below 10 g/ld.) and 72.17% of the patients were having low platelet counts (<150 × 103 /cmm). Our findings are similar with the findings of Advani et al (1999)(3) and Kamps et al. (33,35) 72.5% patients had low WBC counts (<20,000). 20% patients had WBC counts between 20,000-100,000/cm. Total 7.52% patients had WBC counts greater than 100,000cmm at the time of diagnosis.

66.95% patients received BFM- 90 protocol and 33.04% patients received MCP-841 protocol treatment. In our study flow cytometry reports were available for 58 patients. 50 (86.20%) patients were having B-cell immunophenotype. We observed that 31 (62%) patients survived who were having B-cell immunophenotype. Only 8 (13.79%) patients were having T-ALL immunophenotype and 7 (87.5%) patients of T-ALL immunophenotype survived. The survival curve is shown in the figure Ia and Ib.

Most of the patients 67 (58.2%) had normal (5-40 U/L) Serum SGPT levels. 48 (43.7%) patients had higher (>40 U/L) SGPT levels. CR for both the treatment protocol was achieved in 113 (98.2%) patients. EFS and OS of patients treated as per BFM-90; our study revealed that at the end of the study (October 2015), both the OS and EFS were found to be same i.e. 62.8%. While for patients treated as per MCP-841 protocol, our study suggested that at the end of the study (October 2015), both the OS

and EFS were found to be same i.e. 50%. Our study results of EFS and OS are consistent with other studies. The survival curve is shown in figure II

None of the patient relapsed underwent stem cell transplantation. There were no survivors in second CR. Hence the EFS and OS are the same

In the study done in Germany for BFM-90 protocol, the 8-year EFS was 75.9% in while a study done by the UKALL XI, the 8- year EFS was 61% and the OS was 81% (36,37). A study done by Dutch DFCI group, reported that the 7-year EFS rate was 89%, and the 8-year EFS rate was 78.6%.(35,38)

Other studies carried out in India suggested that the overall survival at the end of five years was 53%; EFS was 49% and CR was 91.3 % (33). A study conducted in Netherland showed that the Overall Survival at the end of five years was 83%; EFS was 73% and CR was 99 %(35)

In a study conducted at the Tata Memorial Hospital on 623 children diagnosed with ALL, disease free survival was 56.5% by the Kaplan Meier estimate, and the EFS was 49%(39) Factors such as age, male sex, T-phenotype, high WBC counts are important variables which affects EFS and OS.

In our study, 30 (26%) patients died of relapse. A study carried out by Nachman et al at CCG concluded the 5 years EFS and OS for BFM-90 were 68± 3% % and 77 ± 3% respectively which are consistent with our results of 5 year EFS and OS. (40,41) Result of our study suggests that BFM-90 protocol shows higher rate EFS and OS. Thus BFM-90 protocol is found to be more effective in terms of EFS, OS and CR than the MCP-841 protocol.

Many recent studies done in India from different areas have shown improvement in EFS and OS in ALL patients. Though better supportive care, more intensive treatment will further help to improve the same

Conclusion:

Age, hemoglobin, White blood cell count and platelet count define the risk group suggesting the prognostic features for ALL patients in India. Complete Remission,

EFS and Overall Survival rates achieved represent a significant improvement in ALL patients. Our study indicates that BFM-90 has a higher rate of EFS and OS as compared to MCP-941 protocol. Moreover, MCP-841 had higher number of events as compared to BFM-90.

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