INTRODUCTION

Breast cancer ranks as the first malignancy affecting females, contributing 30% of all females cancer. Breast cancer is second (only to lung cancer) as a cause of cancer death in females. Almost one of every three affected females will die of the disease ***(El-Bolkainy et al., 2008)***.

About 20-85% of the female patients diagnosed with cancer breast, depending on the initial stage, tumor biology and treatment strategy used will develop distant metastases within 5 years of their initial diagnosis. Once metastases are detected, the median survival is in the range of 18-24 months ***(Harold et al., 2008)***.

Metastatic breast cancer is a systemic disease requiring specific strategies to control disease progression and related symptoms. Treatment can assure a significant prolongation of survival, symptomatic control and maintenance of quality of life ***(Orlando et al., 2006)***

Number of recent preclinical and clinical studies have explained conventional chemotherapeutic drugs as angiogenesis inhibitors ***(Miller et al., 2003)***.

Neoangiogenesis play a key role in tumor progression. Tumor cells may induce angiogenesis via the

release of numerous growth factors ex prostaglandin, and by their attraction of inflammatory cells which in turn release multiple angiogenic stimuli ***(Weidner, 2004)***

Vascular endothelial growth factor (VEGF) is an angiogenic polypeptide that is detected in a large variety of malignant human tumors including breast, brain, lung and gastrointestinal tract tumors. Values of VEGF demonstrate a correlation with tumor bulk. Patients with disseminated breast cancer have higher serum VEGF concentration than those with localized disease ***(Colleoni et al., 2002)***.

Chronic administration of lower doses and more frequent schedules of cytotoxics (metronomic delivery) have been tested, in order to optimize the anti-angiogenic effects, to minimize toxicity and over come the repair of endothelial cells ***(Bacci et al., 2005)***.

In fact ***Browder et al. (2006)*** have shown that chemotherapeutic drugs given at a maximum tolerated dose (MTD) can cause apoptosis of the tumor associated vessels but this damage can be repaired rapidly during the prolonged recovery period necessary for myeloid recovery following MTD chemotherapy. Hence by giving chemotherapy more frequent, daily, weekly or twice weekly the endothelial cells repair process can be

compromised and the potential effect of chemotherapy is enhanced.

Metronomic chemotherapy targets the tumor endothelial cells, rather than the cancer cells. Endothelial cells are found in the tumor′ s blood vessels and by killing that endothelial cells, the blood supply is cut off, so tumors without blood supplies remain very small ***(MayoClinic.com, 2006)***

Metronomic chemotherapy can be used in people whose cancers are resistant to MTD chemotherapy because cancer cells are constantly mutating, they may become resistant to chemotherapy drugs, but endothelial cells are genetically stable, which mean that they do not mutate and can not become drug resistant. Even though a drug may no longer be effective against cancer cells, the same drug can still be useful in targeting the endothelial cells ***(Colleoni et al., 2002)***.

The major aim of chemotherapy in patients with metastatic breast cancer is primarily palliative, indeed, the target of chemotherapy in such patients is to obtain maximum symptom control, prevent serious complications and increase survival without diminishing quality of life.

Several chemotherapeutic agents are used for that purpose including Taxanes, Vinorelbine, Capcitabine and Gemcitabine, that agents are used at the MTD are often costly and associated with sever side effects requiring hospitalization, so patients attitudes to receive toxic chemotherapy regimens for metastatic breast cancer are often negative ***(Orlando et al., 2006)***.

Thus the introduction of newer approaches, having improved or at least equivalent efficacy but reduced toxicity and less costly are highly desirable. Such approaches could include using less toxic drugs, more convenient route of administration (oral) and home based (out patient) rather than hospital based therapies ***(Bacci et al., 2005)***.

Colleoni et al. (2002) tested oral metronomic chemotherapy regimen in treatment of metastatic braest cancer patients and reported an impressive efficacy using generally well tolerated protocol. Cyclophosphamide was administrated at a dose of 50mg/day every day, with no breaks and Methotrexate on day 1 and 2 orally (2×2.5mg/day) every week.

Encouragingly, the overall clinical benefit was 31.7%. This was achieved in absence of any serious adverse events, so it is obvious that Cyclophosphamide-Methotrexate

metronomic regimen represent a potentially significant effective treatment for metastatic breast cancer ***(Colleoni et al., 2002)***.

The optimum chemotherapy for metastatic breast cancer is controversial as almost all new chemo-therapeutic drugs give no change in overall survival. Among these drugs is Vinorelbine which when combined with Cisplatin give overall response rate 50-65% when used as first line in metastatic cancer breast even if previously treated with Anthracycline. The economic evaluation carried out by Leung et al 1999 had established that for patients with metastatic breast cancer pretreated with Anthracycline, Vinorelbine is more cost-effective than Taxanes, (Paclitaxel is two times costly than Vinorelbine, Docetaxel is three times costly than Vinorelbine) so the favorable economic profile of Vinorelbine-Cisplatin regimen was primary due to lower cost of the drug, shorter administration time, minimal pre-treatment medication and better toxicity profile in comparison to Taxanes ***(Leung et al., 1999)***.

AIM OF THE WORK

Primary end point:

To asses the response and tolerability of metronomic Cyclophosphamide, Methotrexate regimen in patients with metastatic breast cancer.

Secondary end point:

To evaluate the effect of that metronomic regimen on progression-free survival and over-all survival.

The results will be compared with retrospective results of 50 patients with nearly the same eligibility criteria received Vinorelbine-Cisplatin regimen as a palliative treatment for metastatic breast cancer.

METASTATIC CANCER BREAST

Metastatic (stage IV) breast cancer is defined by tumor spread beyond the breast, chest wall, and regional lymph nodes. Tumor dissemination can occur through blood and lymphatic vessels and via direct extension through the chest wall. The most common sites for breast cancer metastasis include the bone, lung, liver, lymph nodes, chest wall, and brain. However, case reports have documented that breast cancer dissemination to almost every organ in the body (***Carlson et al., 2007)***.

Hormone-receptor "positive tumors are more likely to spread to bone as the initial site of metastasis; hormone-receptor "negative and/or HER-2-positive tumors are more likely to recur initially in viscera. Lobular (as opposed to ductal) cancers are more often associated with serosal metastases to the pleura and abdomen. Most women with metastatic disease have been initially diagnosed with early stage breast cancer, treated with curative intent, and then experience metastatic recurrence. Only about 10% of newly diagnosed breast cancer patients in the United States have metastatic disease at presentation (***Fisher et al., 2005)***.

Symptoms of metastatic breast cancer are related to the location and extent of the tumor. Common symptoms or physical examination findings include bone discomfort, lymphadenopathy, skin changes, cough or shortness of breath, and fatigue. These clinical findings are all nonspecific, and appropriate evaluation is warranted in breast cancer patients with new or evolving symptoms. In some cases, physical examination or radiological findings will demonstrate unequivocal evidence of metastatic breast cancer. In instances when radiologic or clinical findings are equivocal, tissue biopsy is imperative. If a biopsy is performed, ER, PR, and HER-2 should be redetermined **(*Goldhirsch et al., 2005)***.

Detection of metastasis after primary treatment of breast cancer

International figures suggest that about 30% of women will develop recurrence after treatment for primary breast cancer, figures for early stage disease being lower ***(Harold et al., 2008)***.

Follow up of breast cancer patients after finishing adjuvant treatment should include providing physical and psychosocial rehabilitation, monitoring treatment effectiveness and short term and long term toxicity,

detecting recurrences and new cancers, and collecting data for research ***(Hiramanek, 2004)***.

Follow up schedules vary internationally. Guide-lines issued by the American Society of Clinical Oncology in 2005 showed that:

Data are sufficient to recommend monthly breast self-examination, annual mammography of the preserved and contralateral breast, annual pelvic examination and PAP smears should be done since patients are on tamoxifen, and a careful history and physical examination every 3 to 6 months for 3 years, then every 6 to 12 months for 2 years, then annually. Patients should be informed regarding sign and symptoms of recurrence. Data are not sufficient to recommend routine bone scans, chest radiographs, hematological blood counts, tumor markers, liver ultra sonograms, or computed tomography (CT) scans ***(Smith, 2005)***.

It is concluded that follow up programs based on regular physical examinations and yearly mammo-graphy alone appear to be as effective as more intensive approaches based on regular laboratory and instrumental tests in terms of timeliness of recurrence detection, overall survival, and quality of life ***(Rojas et al., 2002)***.

Intensive routine follow up protocols in use were based on two hypotheses: (i) that most recurrences are detected at an earlier stage through follow up; and (ii) that the earlier treatment of recurrences offers a better chance of cure, longer survival, or improvement in quality of life.

However, recent data suggest that neither of these hypotheses is correct and that postoperative follow up of patients with breast cancer is costly and time consuming and does not significantly extend survival ***(Hiramanek, 2004)***.

This is explained by the fact that despite considerable effort to detect recurrent disease early, the evidence suggests that only a minority of recurrences are detected at an asymptomatic stage and most patients with recurrence have signs or symptoms as the first indicator of recurrence and that history and physical examination generally provide the first clues to recurrence. Furthermore, most recurrences present at unscheduled appointments and not as a consequence of routine follow up appoint-ments ***(Donnelly et al., 2001)***.

When analyzing the presentation of recurrent breast cancer, a distinction has been made between locoregional and metastatic disease. Metastatic disease is incurable, and

it has been demonstrated that no survival advantage is gained from diagnosing it at an asymptomatic stage by means of routine investigations ***(Harold et al., 2008).***

Regarding early detection and treatment of asymptomatic locoregional recurrence, it has no benefit to overall survival compared with treatment of symptomatic recurrence. Also its association with a better chance of controlling disease symptoms and thereby improving quality of life is also unproven, except for asymptomatic local recurrence after breast conservation surgery, where salvage mastectomy is a well recognized treatment ***(Churn and Kelly, 2001).***

Therefore, since breast cancer recurrence usually presents to an interval clinic, and most cases that are confirmed following a routine review are already symptomatic, the efficacy of routine follow up in hospital outpatient clinics is highly questionable. There is no evidence of optimal follow up strategy, and identification of an optimized follow up strategy will require long term prospective clinical trials ***(Hiramanek, 2004).***

Monitoring the disease course in patients with metastatic disease is better done with physical examination or imaging studies that directly measure

tumor size. The major exception is bone metastases. In this setting, frequently improvement in pain is the earliest and best measure of the success of systemic or locally directed therapy. Bone scans may show new lesions early in the course of a successful treatment program due to healing of previously undetectable metastatic deposits. Likewise, using bone radiographs to follow radiographically visible lesions can be complicated. New blastic lesions or blastic responses in previous sites of lytic metastases may be due to healing, whereas the radiologist may attribute such findings to disease progression. The oncologist should review such films carefully with the radiologist and provide appropriate interval history to the radiologist when ordering such studies ***(Wood et al., 2005).***

Goal of treatment in metastatic breast cancer:

For many cancers, cure is the expected goal of treatment, particularly if the cancer is diagnosed at an early stage. However, cure is an unlikely outcome for women with metastatic breast cancer; as a result, other goals are of greater importance. These include relief of symptoms, improved QOL, longer survival, and a longer progression-free or relapse-free survival ***(Wood et al., 2005).***

A small fraction of patients, often those with limited sites of metastatic disease or bearing tumors with exquisite sensitivity to treatment, may experience very long periods of remission and tumor control ***(Carlson et al., 2007).***

For women with early breast cancer, a recurrence is most likely within the first five years after treatment, but can still occur up to 30 years later. Cure is possible, but it is very uncommon in women with metastatic breast cancer. A few women who have a complete remission may be long-term survivors. However, tumor growth could be prevented for prolonged periods (five to ten years) ***(Greenberg et al., 2000).***

Despite the disappointing cure rate, treatment prolongs survival in women with metastatic breast cancer. The average length of survival for women treated for

metastatic breast cancer has improved over the last 20 years and is approximately 24 months, although the range extends from a few months to many years. Survival tends to be slightly longer (by months rather than years) for women whose cancers respond to treatment, compared to those who do not respond (non responders) (***Gennari et al., 2007).***

Sometimes, treatments that do not objectively decrease the amount of breast cancer can stabilize tumor growth; in other words, the tumor persists, but does not progress. Women with stable disease in response to a specific treatment tend to survive longer than women whose breast cancer grows despite treatment (called progressive disease), particularly if tumor size is stable for at least six months ***(Cristofanilli et al., 2004).***

Treatment can improve quality of life (QOL) in women with metastatic breast cancer by minimizing symptoms that are caused by the cancer. Studies suggest that chemotherapy effectively improves QOL despite its associated side effects (***Carlson et al., 2007).***

The response rate for a given treatment is a measure of that treatment's effectiveness. It refers to the proportion of women receiving a specific form of treatment who have a measurable decrease in the amount of breast cancer,

either by physical examination or x-ray studies (e.g., computed tomography (CT) scan or chest x-ray). Generally, the response to treatment is considered to be an objective, measurable indication of benefit from therapy. It is a commonly used endpoint in many clinical trials to assess the activity of new treatments ***(Cristofanilli et al., 2004).***

Although response rates in published studies usually include only the patients who have a complete or partial response to a specific therapy, patients with minor responses and stable disease also benefit from therapy, to a lesser degree. More recently, several clinical trials have designated a new term, "clinical benefit" to encompass complete and partial responders as well as those with minor responses and stable disease ***(Wood et al., 2005)***.

Both the response rate and the clinical benefit rate give an estimate of the likelihood of a woman benefiting from a specific therapy. As an example, if a treatment has a response rate of 60 percent, 60 of every 100 treated women can expect to have a measurable decrease (50 percent or greater decrease) in the amount of breast cancer, as long as treatment is administered on time and in the appropriate doses. Whenever possible, the treatment of metastatic breast cancer is aimed at achieving the highest possible response or clinical benefit rate with the least