Acknowledgement

First and foremost thanks to God.

Words fail to express my deepest gratitude to Dr. Atef Youssef Riad, Professor of Radiation oncology and Nuclear medicine, for his great help, valuable suggestions, and kind supervision throughout this study.

I would also like to express my high appreciation to Dr. Eman Mohamed Elsheikh, Assistant Professor of Radiation oncology and Nuclear medicine for her valuable assistance and continuous support throughout this study.

I'm also very grateful to Dr. Nivine Mahmoud Gad, Assistant Professor of Radiation oncology and Nuclear medicine for her remarkable step by step guidance and indispensible advice throughout this study.

I would also like to express my deep appreciation to Dr. Hatem Mohamed Abdallah, Assistant Professor of Radiation oncology and Nuclear medicine for his bright ideas and intelligent recommendations which constantly improved my performance.

List of contents

Introduction ----------	**1**
Aim of the Work ----------	**3**
Review of Literature ----------	**4 - 65**
Epidemiology and Pathogenesis	4
Evaluation of the metastasis	6
Prognostic and Predictive Factors	10
Treatment	13
Treatment Algorithims	14
Treatment lines: Surgery	20
Radiotherapy	25
Hormonal therapy	26
Molecularly targeted therapy	38
Convential Chemotherapy	48
Non-FDA approved novel drugs & trials	64
Patients and Methods ----------	**66**
Results ----------	**81**
Discussion ----------	**109**
Summary ----------	**127**
Conclusion and Recommendations ----------	**130**
References ----------	**131**
Arabic Summary ----------	

Gemcitabine/cis-platin in the treatment of metastatic breast cancer patients pretreated with anthracyclines

Thesis

Submitted for partial fulfillment of the M.D. Degree in

Radiation Oncology and Nuclear Medicine

By

Amr Shafik Tawfik

M.B., B.Ch., M.Sc.

Supervised by

Prof. Dr. Atef Youssef Riad

Professor of Radiation Oncology and Nuclear Medicine department
Faculty of Medicine, Ain Shams University

Dr. Eman Mohamed Tawfik Elsheikh

Assistant Prof. of Radiation Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Dr. Nivine Mahmoud Ahmed Gado

Assistant Prof. of Radiation Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Dr. Hatem Mohamed Abdallah

Assistant Prof. of Radiation Oncology and Nuclear Medicine
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2010

دور عقاري الجيمسيتابين والسيسبلاتين في علاج أورام الثدي المنتشر للمرضى المعالجين قبلا بالأنثراسيكلين

رسالة مقدمة

توطئة للحصول علي درجة الدكتوراه
في علاج الأورام بالإشعاع والطب النووي

من

الطبيب/ عمرو شفيق توفيق
بكالريوس الطب و الجراحة
ماجستير علاج الأورام بالإشعاع و الطب النووي

تحت إشراف

الأستاذ الدكتور/ عاطف يوسف رياض
أستاذ علاج الأورام بالإشعاع والطب النووي
كلية الطب – جامعة عين شمس

الدكتورة/ إيمان محمد توفيق الشيخ
أستاذ مساعد علاج الأورام بالإشعاع والطب النووي
كلية الطب – جامعة عين شمس

الدكتورة/ نيفين محمود أحمد جادو
أستاذ مساعد علاج الأورام بالإشعاع والطب النووي
كلية الطب – جامعة عين شمس

الدكتور/ حاتم محمد عبد الله
أستاذ مساعد علاج الأورام بالإشعاع والطب النووي
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس
٢٠١٠

Introduction

Metastatic breast cancer "MBC" represents 10% of newly diagnosed breast cancer patients. Moreover, a substantial portion of the early and localized breast cancer patients will metastasize sooner or later along the course of their disease.[1]

Multiple hepatic lesions, bone deposits, pulmonary lesions and regional lymph nodes enlargement are typical of MBC, especially in patients who have previously been considered at high risk for recurrence.[2]

In spite of major advances in screening, surgery, radiation, endocrine therapy and chemotherapy of patients with early stage breast cancer, modest progress has been achieved in improving survival for women with metastases. The median survival for patients with metastases remains between 18 and 24 months.[3]

The primary objective of different lines of treatment for MBC patients is palliation, not cure. Treatment aims at controlling the progression of the patient's disease, improve quality of life "QOL" and improve or eliminate tumor-related symptoms.[4]

Endocrine therapy of MBC patients achieves objective response in more than 30% of patients that generally lasts an average of 1 year which is usually several months longer than response to chemotherapy when used in the same setting.[5]

However, with the overall response rate "RR" to chemotherapy being higher than that to endocrine therapy, patients with rapidly progressive tumors or major tumor-related symptoms should be considered for chemotherapy.[6]

Response rates to initial chemotherapy with anthracyclines, taxanes and capecitabine usually range from 25% to 60% with six months median time to progression.[7]

In general, RRs diminish by half when using the agents as second- and third-line treatment, although there is a great variability among trials. It's also noted that multi-drug regimens of active agents consistently show improved RRs that average approximately 20% higher than those for single agents.[6]

Trastuzumab, a humanized monoclonal antibody directed against the extracellular domain of the transmembrane glycoprotein Her2, provides clinicians with a valuable option in the treatment of women with Her2+ve MBC.[8]

Gemcitabine "a pyrimidine antimetabolite" was found to be both effective and safe in combination with different drugs in both locally advanced and MBC.[9]

Heinemann had proved gemcitabine and cisplatin combination to be a highly effective regimen in heavily pretreated patients with MBC.[10]

In 2006**,** the results of Fuentes and colleagues who enrolled 46 patients with MBC to receive gemcitabine and cisplatin as first line therapy showed that 17% of patients achieved complete response “CR” and 64% achieved partial response “PR” with an overall RR of 81%. From this they concluded that gemcitabine plus cisplatin is a highly effective and safe first line treatment for patients with MBC and the time to progression “TTP” of 14.9 months compares favorably with other standard treatments as anthracyclines and taxanes.[11]

Aim of the work

Primary objective

This study was conducted to evaluate the efficacy of gemcitabine and cisplatin combination chemotherapy in MBC patients previously treated with anthracyclines as the first line chemotherapy in terms of degree of response, time to disease progression and treatment related toxicities.

Secondary objective

This study also aims to compare our results with other clinical trials undergone in our center involving MBC.

Epidemiology and Pathogenesis

Breast cancer remains the most frequently diagnosed cancer in women in the United States, accounting for 176,000 new invasive cases yearly and around 41,000 deaths yearly. Breast cancer was also the most common form of cancer seen in Europe in 2006 with 429,900 new cases.[12]

In the United States, the age specific incidence of breast cancer increases with age, to a lifetime risk of breast cancer of 1 in 8 (to 110 years of age); by age of 40, approximately 1 in every 250 women will have been diagnosed with breast cancer annually; at 60 years of age, the figure reaches 1 in 35 women.[13]

Breast cancer accounts for 37.6% of all cancer cases according to the Gharbiah population based statistics. The Cairo's National Cancer Institute gave a similar 37.5% in its institutional based statistics. The clinical oncology department of Ain Shams University gave a lower but still significant frequency of 28.1%.[14]

Incidence rates rose 21% from 1973 to 2000 which is most likely reflecting the increase in usage of mammographic studies, but it then began to decline mostly due to the decrease in using of post menopausal hormone replacement therapy. Mortality rates have stayed relatively constant until recently, when annual decreases have been seen.[12]

Increasing age, family history, and both endogenous and exogenous ovarian hormone exposure have an important effect on risk and have been incorporated into models that predict the individual risk of breast cancer. Diet, alcohol use and other factors play a smaller role.[12]

Inherited genetic mutations in BRCA1, BRCA2, CHEK2 and others, in addition to sporadic epigenetic mutations play a role in the development of breast cancer and recently, it can be directly tested in individuals.[12]

Despite the significant advances in primary and adjuvant treatment for local breast cancer, many patients suffer from systemic relapse. International figures suggest that about 30% of women will develop recurrence after treatment of primary breast cancer. In addition, metastatic disease is diagnosed at presentation in 10% of women. However, this percentage is much higher in areas with less commitment to the screening programs.[15]

According to standard cancer models, tumors are composed of heterogeneous mixtures of independent subclones, originated by divergent genetic mutations; only selected clones can migrate and form metastases. The metastasis is predicted to be a homogeneous monoclonal expansion of an individual subclone, which in turn can accumulate further mutations and diverge even further from the primary tumor. Overall, the model predicts that primary tumors and corresponding metastases are substantially different.[16]

Another model is called the Cancer Stem Cell "CSC" model. It assumes that intratumoral heterogenesity is caused mainly by cell differentiation and that only CSCs can migrate and form overt metastases, while differentiated cells undergo apoptosis. In the CSC model, metastatic cancer tissues undergo differentiation programs that closely resemble those observed in the corresponding primary tissues. Experimental evidence based on gene-expression microarrays tends to support the CSC model for human epithelial tumors, such as breast and colon cancer. The two hypotheses are not mutually exclusive, and elements of both are probably true.[16]

Evaluation of the metastasis

Breast cancer can disseminate to almost any organ of the body. HR+ tumors are more likely to spread to bone as the initial site of metastasis while HR- and/or Her2+ tumors are more likely to recur initially in the viscera. Lobular (as opposed to ductal) cancers are more often associated with serosal metastases to the pleura and abdomen. The symptoms and signs of this metastasis will correlate with its location and extent.[13]

Regarding the primary sites of metastases at time of recurrence; bone metastasis represents 40-75% of cases, followed by locoregional recurrence 15-40%, lung metastasis 5-15%, pleura 5-10%, liver metastasis 3-10% and brain metastasis accounting for less than 5%.[17]

Evaluation of suspected metastasis

Many patients present with nonspecific symptoms, such as new pain, weight loss or dyspnea. Proper examination for the signs of metastasis is mandatory. This should be complemented with complete lab-work and radiological assessment including CT scans, MRIs and bone scan.[12]

Whenever possible, tissue acquisition for diagnostic confirmation should be considered, as not all clinically suspicious lesions that occur after a diagnosis of breast cancer represent metastases; the differential diagnosis should include benign processes and second malignancies. A biopsy is indicated at the time of first suspected recurrence in women with a prior history of breast cancer. Solitary pulmonary nodule particularly requires biopsy, since up to 50% of them represent primary lung cancers, especially with history of smoking.[13]

Repeated biopsy may also permit a more precise characterization of relevant predictive factors. In a large Canadian study, 21% of relapsed tumors had changes in either ER/PR or Her2 status. It is therefore important that tissue confirmation, Her2 analysis and HR evaluation should be considered the standard of care in patients with clinical/radiological suspicion of metastatic recurrence whenever possible.[18]

Furthermore, Broglio and colleagues in MD Andersson Cancer Center published a trial in 2008 which proved that discordance in triple-receptor expression between primary tumor and metastasis also carries a worse prognosis compared to concordance.[19]

Monitoring therapy

Careful assessment of the response to each regimen will assure optimal selection and duration of therapies. If symptom palliation is the main objective, clinical history alone may suffice to determine the success of therapy. Physical examination may also allow response quantitation if disease is easily accessible.[13]

In other patients with more subtle disease signs and symptoms, serial changes in circulating tumor markers or radiographic studies are essential in establishing the response to therapy.[20]

Tumor markers:

Serial assay of serum tumor markers; the older CA15-3 and the newer CA27.29, both products of the MUC-1 gene can aid in response assessment, particularly if disease sites are unassessable by the usual criteria. Serum levels of these

markers are elevated and correlate with disease course in 75 to 90% of patients during therapy.[21]

Up to 20% of patients successfully treated with systemic therapy may experience a transient increase (marker "flare") during the first months after treatment initiation due to release of antigen by cytolysis. Patients with abnormal liver function may also have falsely elevated marker levels because they are cleared by the liver.[20]

Serial tumor marker assay can be helpful in detecting a change in response to treatment. Three to six months after therapy, progressive elevation of marker levels by more than 25% on two separate occasions several weeks apart indicates disease progression in more than 75% of patients.[22]

In the ASCO practice guidelines, monitoring selected patients with metastatic disease in the absence of readily measurable disease was the sole recommended use for circulating tumor markers.[23]

Radiographic studies:

Serial plain radiographs, CT scans or MRIs can permit assessment of tumor response. Bone scans, while helpful, may also be misleading. Technetium phosphonate accumulates in areas of osteoblastic activity rather than in cancer cells. Under therapy, a "scintigraphic healing flare" may appear as early as two months, and persists for as long as 12 months after initiating therapy.[13]

Few trials are available regarding the value of serial PET scans in MBC. One of them was a Belgium trial in which PET scan response in MBC to bone was found to be related to treatment outcome.[24]

Circulating tumor cells (CTC) levels:

From 20% to 45% of patients with primary operable breast cancer and 70% of patients with metastatic disease have disseminated tumor cells (DTCs) that can be detected in bone marrow or in lymph nodes. The need for a relatively invasive procedure (a bone marrow biopsy) and the lack of sufficient specificity and sensitivity as well as method standardization has prevented the routine use of such information in clinical decision making.[13]

With baseline CTC levels measured by withdrawal of 7.5 ml of blood and tested using Cell search system, it is easier to detect DTCs and even to correlate with Progression Free Survival "PFS" in patients with MBC. Data analysis is ongoing to confirm that persistent CTC levels 5/7.5 ml correlate with a lack of treatment efficacy and therefore is a reliable surrogate marker of disease responsiveness.[25]

In a prospective double-blinded multicenter trial, elevated CTCs at baseline predicted a significantly shorter PFS (3 versus 7 months) and Overall Survival "OS" (10 versus 22 months) compared with the finding of fewer or no detectable CTCs. Furthermore, when CTCs were measured within three to five weeks of instituting a new cytotoxic therapy, persisting high levels of CTCs predicted which patients were likely to be receiving ineffective therapy.[26, 13]

However, an ASCO expert panel concluded that data were insufficient to recommend the routine use of CTCs in patients with MBC, pending additional validation Inspite that the Cell Search assay for CTCs is now approved in the US and is commercially available.[20]

Prognostic and Predictive Factors

Classical prognostic factors

The site and number of metastasis is a relevant prognostic factor. Patients with isolated metastases involving lymph nodes or bones may have prolonged disease-free survival "DFS" in contrast to women with hepatic and/or pulmonary disease.[27]

Metastasis-free interval is an easy multifactorial prognostic index reflecting the multiparametric variability of the disease. A relapse-free interval of 5 years is more favorable than a shorter time to progression.[28]

Age and performance status at diagnosis also have a prognostic implication. Low tumor grade is a favorable prognostic factor.[29]

Prior adjuvant therapy, prior therapy for metastatic disease and the duration for response to the metastatic therapy are extremely useful prognostic tools.[12]

HR status and Her2 over expression are adverse prognostic factors associated with tumor aggressiveness. In a French retrospective study of 511 patients with MBC treated at Centre Jean Perrin from 1973 to 2006, OS and DFI analysis of three phenotypes: HR-/Her2- (triple negative); HR+/Her2- (luminal) and Her2+ over expression (Her2+) showed that luminal phenotype patients had the best OS; Her2+ phenotype had an intermediate OS, and triple negative phenotype had the worse OS.[30]