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TABLE OF CONTENTS

Review Article: Management Of Metastatic Breast Cancer (MBC)

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Abstract

Chemotherapy of metastatic breast carcinoma so far, is not curative using the currently available chemotherapeutic, hormonal or biologic agents. The treatment of metastatic breast cancer is aimed mainly at alleviation of symptoms rather than cure. The first choice of therapy is dependent on patient age, performance status, hormone receptor status, human epidermal growth factor receptor-2 (HER-2), involvement of the viscera, or enrollment of patients in investigational trials. Combination of chemotherapeutic drugs showed an advantage for survival, tumor response and time to progression with adverse effects of these agents. It is very important, therefore, to balance between the benefits of treatment and the adverse effects and complication of therapy.

Keywords

chemotherapy, metastatic, HER-2, breast, combination

Introduction

Metastatic breast cancer is not curable by current treatment modalities, although temporary regression of the disease is attainable in about 65% of the patients. Clinical complete remission is observed in less than 20% of the patients but rarely of long duration. Median survival is of about 2 years. The goal of the treatment, therefore, is to palliate the symptoms of the patients and if possible prolongation of useful high quality life. Surgery and radiation therapy play a limited role in patients with metastatic breast cancer as to make a histological diagnosis or mastectomy to prevent local complications. Hormonal therapy, chemotherapy, monoclonal antibody therapy and combination of these agents have proved useful in the management of metastatic breast cancer. Since metastatic breast cancer is incurable and at present time there is no gold standard chemotherapy, we must emphasize early detection of breast cancer and to continue clinical researches to improve the outcome of metastatic breast cancer.

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Definition of MBC

The staging of breast cancer changes with time to reflect the extent of the disease and the prognosis as well as to incorporate the increasing use of novel imaging and pathology techniques employed at diagnosis. The number of lymph nodes involved as strong prognostic factor contributed to these changes. Haggensen and Stout in 1943 said supra-clavicular lymph nodes make patients inoperable. In 1987 The American joint committee on cancer (AJCC) considered supra-clavicular lymph nodes as M1 to reflect poor prognosis.[1] The American joint committee on cancer (AJCC) implemented a revision of the cancer staging containing important changes and additions in the TNM staging system for breast cancer. The rationale for changes and additions stemmed from continuing development in the field of breast cancer diagnosis and management. This revision defined metastatic breast cancer (stage IV) as any T, any N but M1. Metastasis to ipsilateral supraclavicular lymph nodes is no longer considered M1 metastasis.[2]

Clinical trials and end points definition:

Overall survival (OS) is defined as the time from randomization to death from any cause and has been regarded as the gold standard measure

of clinical benefit. Progression-free survival (PFS) is defined as the time from randomization to tumor progression or death from any cause. Time to progression (TTP) is defined as the time from randomization to cancer progression.[3,4,5] The outcomes from meta-analysis of phase III trials, total of 73 trials, only 12% demonstrated an OS and 52% reported significant outcome in the form of PFS or TTP. Similar outcome from another meta-analysis, total of 76 trials, reported only 19.7% of trials demonstrated OS gain. The third meta-analysis, total of 63 trials, only 13% demonstrated OS benefit. These findings indicate that, so far, lack of cytotoxic, biological, and endocrine therapy to clearly prolong overall survival.[3, 4, 6, 7]

Preferred chemotherapy regimens

Metastatic breast carcinoma can be categorized from management point of view to 2 main subtypes: (1) Human epidermal growth factor receptor type2 negative {HER2-} and estrogen receptor negative {ER} disease. There is no randomized phase III trials showing a survival benefit of combinations compared to sequential chemotherapy of the same drugs for this subtype of malignant disease. (2) HER2 positive disease, data support the use of trastuzumab as a single agent or in combination with chemotherapeutic agents.

Chemotherapy is indicated for patient's refractory to hormonal manipulation, as an investigational studies, hormone-receptor negative and for those with an aggressive disease.[8] Several chemotherapy regimens have been used (Table 1). Since their introduction in the 1980s, the anthracyclines, doxorubicin and epirubicin, have been considered to be among the most active agents for the treatment of MBC. Meta-analysis demonstrated that first-line treatment with anthracycline-containing regimens confer a marginal survival benefits compared with non-anthracycline-containing regimens.[9] The taxanes, paclitaxel and docetaxel, have been developed in the 1990s and evaluated in the treatment of anthracyclines-pretreated MBC. Docetaxel significantly improved over all survival (p=0.0097), time to disease progression (p=0.001), and response rate (p<0.0001) compared with mitomycin c plus vinblastine[10] Docetaxel is the only single agent for which a survival benefit has been demonstrated in anthracycline-pretreated MBC.[10]

Other active agents	Preferred combinations	Preferred agents
Gemcitabine	CAF	Anthracyclines: Doxorubicin, Epirubicin
Cis-Platinum	FEC	Taxanes: Paclitaxel, Docetaxel
Etoposide	AC	Capcitabine
Vinblastine	AT	Vinorelbine
	CMF	
	TC	
	TAC	

C= cyclophosphamide; A= doxorubicin; F= 5FU; E= Epirubicin; T= docetaxel; M= methotrexate

Table 1: Preferred chemotherapy regimens for MBC

In 2004, Gemcitabine in combination with paclitaxel demonstrated time to progression benefit in patients with MBC and approved by FDA as first line therapy after adjuvant anthracycline chemotherapy or contraindication to anthracycline treatment .[4,11]

Combination therapy

There are ideal criteria which should be met when combination chemotherapy is chosen for treatment of metastatic breast cancer. These criteria include:

1. Single agent activity
2. Distinct mechanism of action
3. Preclinical evidence of synergy
4. No cross resistance
5. No overlapping toxicity

However, all these criteria are rarely met and consequently many combination chemotherapies have failed to yield better result compared with sequential treatment and combination chemotherapy did not improve over all survival or quality of life compared to sequential therapy.[12,13,14] A major reason for combination chemotherapy failure is related to dose intensity (mg/m2/week). The dose intensity should be reduced in combination treatment to avoid drug overlapping related toxicity and absence of

synergistic activity.

The treatment of metastatic breast cancer with combination chemotherapy prolong survival and improve quality of life but it is not curative. In addition to that, they are toxic, rarely compared in randomized trial and ranked by single parameter [response rate (RR), PFS and TTP] which unlikely will affect over all survival.[4] Therefore, treatments associated with minimal toxicity may be preferred.

Therapeutic advances

Monoclonal antibody therapy

New developments in the treatment of MBC do, however, mean that MBC is increasingly being managed as a chronic disease. Therefore quality of life and the convenience of treatment become important factors in the management of patient with MBC. Trastuzumab is a humanized anti-HER2 monoclonal antibody.HER2, a transmembrane glycoprotein, is over expressed in 20%-30% of human breast cancer[(15)] Trastuzumab is effective and safe as a single agent first-line treatment of patient with HER2 positive MBC.[(16)] When combined with taxane, they represent a rational designed combination treatment. Each component has single agent activity, distinct mechanism of action, evidence of synergy[(17)], non-overlaping toxicities and without cross-resistance. The result of this combination offers a survival advantage in patients with positive HER2 MBC.[(18)]

Combining anti-HER2 therapy with cytotoxic agents as taxane improves the response of patients to treatment with minimal toxicity and improved survival and quality of life. Trastuzumab has been approved by the FDA as a single agent for the treatment of patients with HER2 positive metastatic breast cancer and who have received one or more chemotherapy regimens or in combination with paclitaxel as first line treatment.[(19)] Trastuzumab then has been approved by the FDA as a first-line treatment for MBC in 1998 in combination with paclitaxel. Currently, Trastuzumab-based therapy is the standard of care for HER2 positive MBC.[(4, 20)]

Oral chemotherapy

Capecitabine has a unique enzymatic activation pathway. The drug is preferentially activated to its cytotoxic metabolite, 5FU, within the tumor site. The drug level is at a median level of 3.2 fold higher in the tumor tissues than in surrounding normal tissues.[(21)] This difference is due to higher activity of thymidine phosphorylase in tumor cells than in non-malignant cells. Capcitabine as monotherapy, an intermittent regimen of 1,250 mg/m twice daily, day 1-14 of 21-day cycle is the standard approved regimen. It is approved in USA, Canada and the entire European Union for taxane-pretreated metastatic breast cancer. It is an oral convenient drug used as 2nd line treatment for MBC. The patient should be able to report any side effects, expectations of survival more than 3 months and performance status 0-2.

Hormonal therapy or Chemotherapy or both

Endocrine therapy and chemotherapy are the two major classes of systemic therapy used in the treatment of MBC. Combination of these major types of therapy is not preferred due to many factors as illustrated in Table 2.[(21-25)] Choosing therapy for patient with MBC requires an understanding of the natural history of the disease and careful evaluation of the patient. Multiple factors affect the choice of therapy as illustrated in (Table 3). Premenopausal patients with MBC can be treated with tamoxifen or with

1. Hormone slows the growth of tumors and the tumors become less responsive to chemotherapy.
2. Thrombosis like DVT doubled when both combined.
3. Difficult to differentiate which one has conferred the benefit.
4. Little known about the cytokinetic interaction of chemotherapy and hormonal therapy.

Table 2: Reasons why endocrine and chemotherapy combination are not preferred[32]

Endocrine therapy	Chemotherapy
Old > 35 years	Young < 35 years
Good performance status	Poor performance status
DFI > 1 year	DFI < 1 year
ER/PR positive	ER/PR negative
Non-visceral metastases	Visceral metastases
Grade 1	Grade 3
	HER2 positive

DFI: Disease free interval; ER: Estrogen receptors; PR: Progesterone receptors

Table 3: Factors affecting the choice of endocrine and chemotherapy[32]

Radiation ± steroids	Surgery
Bony metastasis with complications	Investigation of a lesion
Local recurrence	Intervention of complication:
Orbital Metastasis	Hemorrhage/Abscess
SVC obstruction	Treatment of fracture
Brain metastasis	Surgical decompression of spinal cord
Symptomatic endobronchial tumor	Solitary lesion

SVC: superior vena cava.

Table 4: Indications for surgical and radiotherapy

ovarian ablation if tamoxifen was used as first line therapy. Goserelin and tamoxifen has been used and reported as effective. However, for postmenopausal patients, the options of hormonal therapy include aromatize inhibitors (anastrozole or letrozole), tamoxifen or exemestane.

Bone metastasis secondary to breast carcinoma are important complications and a common causes of morbidity of these patients. These complications include bone pain, bone fractures and spinal cord compressions which can complicate the clinical course of metastatic breast carcinoma. These complications need adequate prevention and intervention to improve the quality of life of these patients. Bisphosphonate by inhibiting the oseolytic activity are effective treatment in preventing complications of metastatic bone diseases and need to be part of the treatment of metastatic breast carcinoma[26-29] A meta-analysis that included randomized trials of 12 studies of bisphosphonate treatment of patients with metastatic cancer of various malignancies demonstrated decreased risk in skeletal related events (SRE) compared with placebo. There was no difference between pamidronate and zoledronate regarding SRE, pain reduction or survival in patients with MBC. However, zoledronate may be superior to pamidronate in reducing bony fracture, hypercalcemia of malignancy and reducing the need for palliative radiation treatment. In addition, zoledronate require shorter infusion time.[30, 31]

The benefits of high dose chemotherapy and bone marrow transplantation as well as immunotherapy were not proved. Alternative therapy in the form of Arabic medicine (quotry, black seed, special food or water) delay treatment and no single study proved its benefit. Surgical intervention and radiotherapy have limited roles in the management of MBC as shown in (Table 4).

Conclusion

Even though breast cancer is increasingly recognized as heterogeneous disease and of several important tumor subtypes with different natural clinical courses requiring different types of treatment, metastatic breast cancer is not curable by current treatment modalities, although temporary regression of disease is attainable in the majority of patients. Clinical complete remission is observed in less than 20% of patients but rarely of long duration with median survival of about 3 years. The goals of the treatment, therefore is to palliate the symptoms of the patients and if possible prolongation of

useful quality life. Surgery and radiation therapy have limited roles in the treatment of MBC as to make histological diagnosis or to prevent complication. Hormonal therapy, chemotherapy, monoclonal antibody therapy or combinations of these treatments have proved useful in the management of MBC. Increased effort at early detection and continuing of clinical researches are most likely to result in improving of the outcome of MBC.

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