Review Article

Management of metastatic breast cancer (MBC)

Ali M. Al-Amri, MD.[1]

[1]Department of Internal Medicine/Oncology, College of Medicine, University of Dammam, King Fahd Hospital of the University, Al-Khobar, Eastern Province, Kingdom of Saudi Arabia.

Address of Correspondence: Dr. Ali M. Al-Amri, MD, Department of Internal Medicine and Oncology, King Fahd Hospital of the University, Al-Khobar 31952, PO Box 40182, Kingdom of Saudi Arabia. Telephone 9663896741, E-mail aliamri49@hotmail.com.

Abstract: Chemotherapy, so far, of metastatic breast carcinoma 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.

[Ali M. Al-Amri. **Management of metastatic breast cancer (MBC).** *Life Sci J* 2012;9(4):597-601] (ISSN:1097-8135). http://www.lifesciencesite.com. 91

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 goals 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.

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]

Recently, 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 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/m^2/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 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 to 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 convenient 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], nonoverlaping 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 improve 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. Nowadays, 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 metastaic 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 majors type 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 ovarian ablation if tamoxifen used as first line therapy. Goserelin and tamoxifen has been used and reported as effective. However, 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 bones 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 the risk of skeletal related events (SRE) compared to 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 for 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 a limited role 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 type 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 and still the 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 high quality life. Surgery and radiation therapy play a limited role 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 improvement of the outcome of MBC.

Table 1. Preferred chemotherapy regimens for MBC

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

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

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

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

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

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

Table 4. Indications for surgical and radiotherapy

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

SVC: superior vena cava.

References

1. Fleming ID, Cooper JS, Henson DE, et al (eds): AJCC cancer staging manual (ed 5). Philadelphia, PA, Lippincott-Raven, 1997
2. S. Eva Singletary, Craig Allred, Pandora Ashley, et al: Revision of the American joint committee on cancer staging for breast cancer. JCO 2002;20:3628-3636.
3. Mathoulin-Pelissier S, Gourgou-Bourgade S, Bonnetain F and Kramar A. Survival end points reporting in randomized cancer clinical trials: A Review of major journals. JCO 2008;26(22):3721-3726.
4. Pazdur R. Endpoints for assessing drug activity in clinical trials. The Oncologist. 2008 ;13(suppl2):19-21.
5. Verma S, Mcleod D, Batist G, Robidoux A, Martins I and Mackey J. In the end what matters most? A Review of clinical end points in advanced breast cancer. The Oncologist2011;16:25-35.
6. Saad ED, Katz A, Buyse M. Overall survival and post-progression survival in advanced breast cancer: A review of recent randomized clinical trials. JCO 2010;28:1958-1962.
7. Wilcken N, Dear R. Chemotherapy in metastatic breast cancer. A summary of all randomized trials reported 2000-2007. Eur J Cancer 2008;44:2218-2225.
8. Norton L. Salvage chemotherapy of breast cancer: Semin Onco 1994;21:19-24.
9. Fossati R, Confalonierri C. Torri V et al. Cytotoxic and hormonal treatment for metastatic breast cancer: J Clin Oncol 1998;16:3439-3460.
10. Nabholtz JM, Senn HJ, Bezwoda WRet al. Prospective randomized trials of docetaxel vrsus mitomycin plus vinblastine in patients with MBC pretreated with anthracyclines. J Clin Oncol 1999;17:1413-1424.
11. Albain K, Nag S, Calderillo-Ruiz G, Jordaan J, LIombart A, Pluzanska A et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with matastatic breast cancer and prior anthracycline treatment. JCO 2008;28(24):3950-3957.
12. Joensuu H, Holli K, Heikkinen M et al. Combination chemotherapy versus single agent therapy as first- and second-line treatment in metastatic breast cancer: a prospective randomized trial. J Clin Oncol 1998;16-3720-3630.
13. Sledge GW, Neuberg D, Ingle J et al. Phase III tria of doxorubicin (A) vs. doxorubicin + paclitaxel (A+T) as first-line therapy for metastatic breast cancer (MBC): an intergroup trial. Proc Am Soc Clin Oncol 1997; 16:1a.
14. Slamon DJ, Godolphin W, Jones LA et al. Studies of the HER-2/neu proto-oncogene in human breast and ovarian cancer. Science 1989;244:707-712.
15. Charles L, Vogel, Melody A, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2 overexpressing metastatic breast cancer. J Clin Oncol 2002;20:719726.
16. Baselga J, Norton L, Albanell J et al. Recombinant humanized anti-HER2 antibody Herceptin enhance the antitumor activity of paclitaxel and doxorubicin against HER2/neu overexpressing human breast xenografts. Cancer Res 1998;58:2825-2831.
17. Slamon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plu a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783-792.
18. Edith A, Perez and Christy A, Russell. Metastatic Breast Cancer: In: Manual of breast diseases,Ismail Jatoi, editor.Lippincott Williams & Wilkins;2002:365-87.
19. Schuller J, Cassidy J, Dumont E et al. Preferential activation of capecitabine in tumor following oral administration to colorectal cancer patients. Cancer Chemother Pharmacol 2000;45:291-297.
20. Goldhirsch A, Coates AS, Gelber RD, et al. First-select the target: Better choice of adjuvant treatments for breast cancer patients. Ann Oncol 2006;17:1772-1776.
21. Priestman T, Baum M, Jones V, Forbes J. Comparative trial of endocrine versus cytotoxic treatment in advanced breast cancer. Br Med J 1977;1:1248-50.
22. Obsborne CK, Boldt DH, Clark GM, Trent JM. Effect of tamoxifen on human breast cancer cell cycle kinetics: accumulation of cells in early G1 phase. Cancer Res 1983;43:358-5.
23. Wood KE, Randolf JK, Gewirtz DA. Antagonism between tamoxifen and doxorubicin

in the MCF-7 human breast tumor cell line. Biochem Pharmacol 1994; 47:1449-57.
24. Fisher B, Redmond C, Brown A, et al. Influence of tumor estrogen and progesterone receptor level on the response to tamoxifen and chemotherapy in primary breast cancer. J Clin Oncol 1983; 1:227-41.
25. Lippman ME. Efforts to combine endocrine and chemotherapy in the management of breast cancer. Do two and two equal three? Breast cancer Res Treat 1983; 3:117-27.
26. Conte PF, Latreille J, Mauriac L et al. Delay in progression bone metastases in breast cancer patients treated with intravenous pamidronate: results from a multinational randomized controlled trial. The Aredia Multinational cooperative group. J Clin Onol 1996:14:2552-1559.
27. Berenson JR, Rosen LS, Howell A et al. Zoledronic acid reduces skeletal-related events with osteolytic metastases. Cancer 2001; 91:1191-1200.
28. Hortobagy GN, Theriault RL, Porter L et al. Efficacy of pamidronate in reducing skeletal complications in patients with breast cancer and lytic bone metastases. Protocol 19 Aredia breast cancer study group. N Engl J Med 1996; 335:1785-1791.
29. Lee S. Rosen, David Gordon, Mary Kaminski et al. Zoleronic acid versus pamidronate in the treatment of skeletal metatases in patients with breast cancer or oseolytic lesions of multiple meloma: A phase III, double-blind, Comparative trial. Cancer J 2001; 7:377-387.
30. Hortobagyi GN, Theriault RL, Lipton A, et al. Long-term prevention of skeletal complications of metastatic breast cancer with pamidronate. Protocol 19 Aredia Breast Cancer Study Group. JCO 1998;16(6):2038-2044.
31. Rosen LS, Gordon DH, Dugan WJr, et al. Zoledronic acid is superior to pamidronate for the treatment of bone metastases in breast carcinoma patients with at least one osteolytic lesion. Cancer 2004;100(1):36-43.
32. Haskell C. Breast cancer. In: Haskell Cancer Treatment. 5th ed. Philadelphia: W. B. Saunders company 2001;507-585.

9/25/2012