Tailoring Treatment Decision-making in Metastatic Breast Cancer

a report by

Nagi S El Saghir[1] *and* **Hassan A Hatoum**[2]

1. Clinical Professor of Medicine and Medical Oncology; 2. Oncology Research Fellow, American University of Beirut Medical Center

DOI: 10.17925/EOH.2008.04.1.62

Advanced breast cancer (BC) includes locally advanced and metastatic disease and constitutes about 6–10% of cases of BC at presentation in industrialised nations and up to 60–80% in developing countries with limited or basic resources, as defined in the Breast Health Global Initiative Guidelines.[1–3] A significant number of patients with primary early BC at presentation continue to relapse and present with metastatic disease. Median survival of patients with metastatic BC (MBC) is between two and three years.[4] Recent data using modern systemic chemotherapy and hormone and targeted therapy give better but still modest results.[5]

Once BC recurs, the goal of treatment of MBC is control of disease and palliation of symptoms for as prolonged a time as possible, with as few adverse effects as possible. This goal of prolonging life quantitatively and qualitatively may translate into improved disease-free survival (DFS) and overall survival. Improvement of overall survival may be achieved in a greater percentage of patients with minimal quantity of disease and so-called oligometastatic BC.

Early-detected local recurrences can be treated with local mastectomy with/without radiation therapy and result in cure.[7] In patients with single-site and oligometastatic BC, modern aggressive therapy has been shown to result in an improvement of survival.[8]

This article will review recent advances in the treatment of MBC and discuss tailoring decision-making in order to achieve maximal therapeutic benefit with least toxicity while having an ultimate goal of palliation and/or cure.

Definitions, Prognosis and Predictive Factors

Although MBC at presentation is chemonaïve, most patients with the more common MBC at recurrence have already had either adjuvant chemotherapy and/or targeted hormone therapy (HT). More than 50% of recurrences occur after five years from diagnosis, with many recurrences reported even after 10 or 20 years or more.[9] Factors that predict early recurrences (within two to three years of diagnosis) include stage of disease, patient age, menopausal status, pathology of tumour, hormonal receptors, HER2 receptors, uPA, gene signature profiles, *tau* gene and *P53* gene, as well as the optimality of treatment modality that was applied at the time of initial diagnosis. Gene microarrays in BC improve prediction of local and distant metastasis,[10–12] as well as local recurrence.

Tailoring of therapy to each individual patient involves making a choice of therapy based on factors that affect prognosis and are known to predict response to the type of available drugs and treatment. These factors include longer versus shorter disease-free interval since diagnosis of primary BC, age, menopausal status, site(s) of recurrence (soft tissue and bone versus visceral), volume of recurrent disease and effects on other organ functions, performance status and significant underlying disease, as well as tumour characteristics such as hormone responsiveness status, HER2/neu receptor status and prior adjuvant therapy. Additional important and practical aspects include availability and accessibility of multiple diagnostic and therapeutic modalities to the patient, as well as the level of resources of the country of residence[1] and the patient's personal preference and resources.

Tailoring Endocrine Therapy for Metastatic Breast Cancer

Endocrine therapy allows disease control, palliation of symptoms and improvement of quality of life. It was started in the 19th century with oophorectomy. In the 1970s oestrogen receptors (ERs) and response to tamoxifen were demonstrated.[13,14] Hormonal sensitivity is guided by the presence of ERs and progesterone receptors (PRs). Newly studied gene profiles may help to predict sensitivity or resistance to HT and include ER and PR interaction with HER2/neu and other pathways.[15] Gene profiling by the 21-gene recurrence score (Oncotype DX) has recently been approved for predicting and quantifying the risk of distant recurrence after adjuvant tamoxifen.[16] Better and longer responses to HT are seen in low-grade tumours with a higher percentage and intensity of HR.[14]

Endocrine therapy is recommended as primary systemic therapy for patients with metastatic disease and positive HRs. Patients with soft-tissue and bone metastases are more likely to have ER-positive tumours.[17] Patients with soft tissue and bone disease respond better to HT than those with visceral disease.[18]

Tailoring Different Hormonal Therapies for Metastatic Breast Cancer in the Post-menopausal Patient

Anti-oestrogens

Until recently, tamoxifen, an anti-oestrogen, was the gold standard of endocrine therapy and had been so for over 30 years. Tamoxifen is the

Nagi S El Saghir is a Clinical Professor of Medicine and Medical Oncology at the American University of Beirut. He has published and lectures on epidemiology and the early detection of breast cancer, as well as the management of breast cancer, particularly in young women. He is a reviewer and member of the Editorial Boards of several international scientific medical journals, and is Speciality Editor of *The Breast* and International Editor for the *Journal of Clinical Oncology*. Professor El Saghir is the author or co-author of over 40 peer-reviewed articles and a book, *ABC of Breast Diseases*, in Arabic. He is co-ordinator of the Breast Tumor Clinic at the American University of Beirut Medical Center. Professor El Saghir graduated from the Free University of Brussels, Belgium, in 1978 and completed his haematology–oncology training at St Luke's-Roosevelt Hospital Center of Columbia University in New York.

E: nagi.saghir@aub.edu.lb

prototype of selective oestrogen receptor modulators (SERMs). It saturates the nuclear ER, blocks the interaction of estrogen with ER and stops the ER-dependent growth of BC cells. It is used orally at a dosage of 20mg per day. Tamoxifen has agonist effects that produce undesirable side effects such as uterine cancer, and favourable side effects such as increased bone density. Toremifene is another SERM that is effective in ER-positive MBC, but it was found to be cross-resistant to tamoxifen and did not gain clinical recognition.[19] Fulvestrant, a pure anti-oestrogen, is a selective oestrogen receptor downregulator (SERD) that destroys ERs and decreases the number of PRs in BC cells.[20] Fulvestrant is now approved for tamoxifen-resistant tumours. It was equivalent to the steroidal aromatase inhibitor (AI) exemestene after failure of non-steroidal AIs (anastrozole and letrozole) where median time to progression (TTP) in both exemestene and fulvestrant was 3.7 months.[21]

Aromatase Inhibitors

Aminogluthetimide (AG) is a first-generation AI that has replaced surgical adrenalectomy.[22] AG is a non-specific AI that suppresses steroidogenesis. Patients receiving it require supplementation of corticosteroids. AIs interfere with peripheral conversion of androstenedione into oestrogens, thus suppressing the sources of oestrogen in the post-menopausal woman. AIs have been shown to be effective in tamoxifen-resistant patients. Anastrozole was shown to produce lesser toxicity and equivalent 56% response rates to tamoxifen.[23,24] Letrozole showed a higher overall objective response of 32 versus 21%, with a clinical benefit of 49 versus 38% and an overall survival of 34 versus 30 months for tamoxifen.[25] Exemestene gives 23% response rate after progression on tamoxifen.[26] AIs gave better results when compared with megesterol acetate.[27–29] AIs are now recommended as first-line HT in post-menopausal women. To be effective, AIs have to induce marked suppression of oestrogens of over 90%. Letrozole has been shown to produce more significant aromatase inhibition. No clinical study has yet shown definite superiority of one agent over the other. Results of an ongoing clinical trial comparing the three agents will be known in a few years' time.[30] After failing to respond to one agent, patients may be switched to another one. The Evaluation of Faslodex versus Exemestane Clinical Trial (EFECT) has recently shown that after progression on a non-steroidal AI (anstrozole or letrozole), the steroidal AI exemestene produces clinical benefit (31.5%) and response rates (6.7%) that are equivalent to fulvestrant (32.2 and 7.4%, respectively).[21]

Progestational Agents

Progestational agents have also been used after failing to respond to tamoxifen. Synthetic megesterol acetate is the most commonly used agent (dosages of 40mg four times daily) and produced response rates in the study, which compared it with exemestene.[27] Megesterol acetate is used after failing to respond to tamoxifen and AIs.

Tailoring Hormone Therapy of Metastatic Breast Cancer in Pre-menopausal Patients

HT is used as a first-line therapy in pre-menopausal women with non-visceral or low-bulk soft-tissue and bone MBC. Ovarian ablation/ovarian suppression (OA/OS) may be achieved by either surgical oophorectomy or irradiation. Patients are usually given tamoxifen in addition to OA/OS. OS is also achieved with a luteinising-hormone-releasing hormone (LHRH) such as goserelin (Zoladex, Leuprolide or Triptorelin). The combination of LHRH with tamoxifen is better than tamoxifen alone, with an overall survival of 2.9 versus 2.5 years.[31] Recent small series have indicated that OA/OS can be successfully combined with AIs in pre-menopausal women with HR-positive MBC,[32] and a recent phase II study of 45 patients showed a 72% clinical benefit (CR: 3% + PR: 34% + stable disease over 6 months: 34%), median TTP of 8 months (range two to 63 months) and median overall survival of 26 months (11 to more than 63 months) with combined overall survival and AI modality.[33]

Tailoring Chemotherapy for Metastatic Breast Cancer

BC is generally considered a chemotherapy-sensitive tumour. Chemotherapy is generally used upfront in patients with negative HRs, hormone-refractory disease and in the presence of rapidly proliferating and advancing disease, visceral disease, high-volume and multiple-site metastasis in patients with positive HRs. Chemotherapy is generally used at regular intervals and cycles that would cause maximal cell kill with limited reversible toxicity on normal tissues. Recent data indicate that low-dose daily or weekly metronomic chemotherapy may have additional antiangiogenic mechanisms of action.[34] Most effective agents include anthracyclines and taxanes, which give 60–70% response rates. Other effective agents include fluorouracil, capecitabine, vinorelbine, cyclophosphamide, gemcitabine and platinum salts.[35,36] Taxanes are useful in patients who have tumours that are resistant to anthracyclines.[37] Recent data show that weekly paclitaxel is better than a three-weekly regimen and it is recommended to be used as such.[38] Newer taxanes include nanoparticle-albumin-bound paclitaxel (nab-paclitaxel: Abraxane), which produces higher response rates than paclitaxel (33 versus 19%). It has no hypersensitivity reactions but induces more neuropathy.[40]

Combination versus Sequential Use of Chemotherapy in Metastatic Breast Cancer

Combination chemotherapy includes fluorouracil plus doxorubicin plus cyclophosphamide, cyclophosphamide plus epirubicin plus fluorouracil, doxorubicin plus cyclophosphamide (AC) or epirubicin plus cyclophosphamide (EC), doxorubicin plus docetaxel or doxorubicin plus paclitxel (AT). Combination AT versus AC was studied and no survival advantage noted.[41] Taxanes combined with doxorubicin[42] showed a longer TTP. Docetaxel combined with adriamycin and cyclophosphamide gave more significant toxicity.[43] On the other hand, significant overall response rate (ORR) (42 versus 30%), TTP 6.1 versus 4.2 months and overall survival advantage of 14.5 versus 11.5 months was reported with the combination of docetaxel plus capecitabine versus docetaxel as a single agent.[44]

Another approved combination is gemcitabine plus paclitaxel, which produced a significantly higher ORR of 40.8 versus 22.2%, TTP 5.2 versus 2.9 months and overall survival of 18.5 versus 15.8 months versus single-agent paclitaxel in a phase III trial.[45] Gemcitabine combined with vinorelbine compared with single-agent vinorelbine in a phase III study of patients refractory to anthracyclines and taxanes with heavy visceral disease showed a non-statistically significant ORR of 36 versus 26% and significant PFS of six versus four months, but with a higher haematological toxicity.[46] Vinorelbine is an effective agent in MBC and has been combined with cisplatin in phase II studies.[47] Platinum compounds are getting more attention for triple-negative disease. However, no definite data are yet available. The

combination of ixabepilone (Ixempra), a new semi-synthetic epothilone analogue with capecitabine, produced 35 versus 14% objective response rates in heavily pre-treated patients progressing after anthyracyclines and taxanes,[48] and is now approved for use in patients with anthracycline and taxane-resistant tumours.

Although combination chemotherapy is generally more active and produces higher response rates and longer TTP, most patients receiving single-agent chemotherapy use other drugs after progression, and most studies did not have a planned cross-over analysis. Such a study comparing anthracyclines with taxanes in combination or in sequence did not show an improvement of TTP or survival.[49] Combinations are used more in younger patients, who have a better tolerance than older patients, in the presence of a more aggressive disease and for more bulky visceral involvement. Otherwise, sequential administration of drugs, particularly anthracycline and taxanes, is preferred.

Tailoring Duration of Chemotherapy to Response and Toxicity in Metastatic Breast Cancer

Patients are usually evaluated for the palliation and disappearance of symptoms and signs of disease, as well as tumour markers and imaging studies. If the patient shows improvement after two to three cycles of a certain chemotherapy regimen, it is continued for a total of six to eight cycles. The exact total duration of therapy depends on the response and toxicity profile of the drugs used. Anthracyclines are limited by potential cardiotoxicity. Dexrazoxane, an iron chelator, has been shown to reduce anthracycline-related cardiac toxicity[50] and is approved for patients receiving more than 300mg/m^2 of doxorubicin. Pegylated doxorubicin has similar results to doxorubicin for ORR, PFS and overall survival and produced less cardiac toxicity than doxorubicin.[51] There are no data to show advantages for maintenance chemotherapy and it is generally not recommended. Once patients complete their planned and tolerable therapy they are placed under observation if they have negative HRs, or placed on HT if they have positive HRs. Duration of targeted therapy is discussed below.

Trastuzumab is more effective when used in combination chemotherapy with anthracyclines, cyclophosphamide and taxanes, and gives an added survival advantage over chemotherapy.

Targeted Therapy in Metastatic Breast Cancer

Patients with MBC whose tumours show overexpression of HER2/neu cell surface receptors by IHC+++, or who have amplification of the corresponding HER2 gene when HER2/neu is borderline by IHC (two plus), benefit from anti-HER2-targeted therapy. Trastuzumab is a new humanised monoclonal antibody that targets the extracellular domain of HER2 cell surface receptors and gives 17% ORR in MBC. It has been shown to result in prolonged overall survival as a first-line therapy for MBC patients.[52] Trastuzumab is more effective when used in combination chemotherapy with anthracyclines, cyclophosphamide and taxanes, and gives an added survival advantage over chemotherapy.[52-54]

Combination treatment with chemotherapy is preferred over trastuzumab monotherapy because of a higher response rate, reaching 60–70% for the combination[55] compared with 20–30% for monotherapy.[56,57] Excessive cardiac toxicity was noted when used with anthracycline,[58,59] and concurrent use of trastuzumab with anthracycline is avoided. Trastuzumab is more safely combined with taxanes.[60] A trastuzumab plus docetaxel combination gave a 73% ORR with a median TTP over 10 months in the BCIRG 007 trial, where carboplatin gave no further benefit in the trastuzumab + docetaxel + carboplatin arm.[61]

Dosing and Duration of Trastuzumab in Metastatic Breast Cancer

Trastuzumab is generally continued until disease progression in the metastatic setting. The safety profile of trastuzumab allows for continued administration as long as patients are monitored by repeated echocardiography and ejection fraction every two or three months. The cardiac toxicity of long-term administration of trastuzumab remains unknown.

Tailoring Targeted Therapy After Progression on Trastuzumab

Synergism with chemotherapy is cited as a possible reason for continuation of trastuzumab with other combinations of chemotherapy at time of progression. Because of potential risks of cardiotoxicity and its high cost, it is often discontinued and replaced by other drugs. There was no prospective data-based evidence about this issue[62] until very recently, when lapatinib plus trastuzumab was shown to be better than lapatinib alone. New targeted therapy for trastuzumab-resistant HER2/neu-positive tumours includes lapatinib, pazopanib and pertuzumab.[62a]

Lapatinib

Lapatinib is an oral 4-anilinoquinazoline derivative and a reversible dual tyrosine kinase inhibitor that affects HER1 and HER2/ErbB2.[63] Trastuzumab-resistant HER2-positive cells may remain sensitive to lapatinib. Combining lapatinib with anti-HER2 antibodies may produce synergistic effects and enhance apoptosis in BC cells with Her-2 overexpression in different studies.[64]

Lapatinib combined with capecitabine was associated with a 51% reduction in the risk of disease progression and a median PFS time of 37 weeks, compared with 18 weeks in the capecitabine single-agent arm. ORR for the combination therapy group was 23% compared with 14% in the monotherapy group (p=0.113). The combination therapy group had a tendency to experience fewer progressive central nervous system (CNS) metastases (11 versus four). Lapatinib is a small molecule that crosses into the cerebrospinal fluid. The effect in reducing CNS metastases has been shown in another phase II trial.[65] Lapatinib is now approved for use in trastuzumab-resistant patients and is being investigated for first-line therapy.

Pertuzumab

Pertuzumab is a new monoclonal antibody that binds to the dimerisation domain of the HER2/neu receptor and prevents pairing and homodimerisation of HER2, as well as heterodimerisation of the other HER receptors – HER1, HER3 and HER4 – and is a potentially active monoclonal antibody in trastuzumab-resistant and HER2-positive BC. Recent safety data on pertuzumab were favourable, and

evidence of activity (ORR of 18.2% and clinical benefit rate of 39.4%) was seen in 33 patients enrolled in a phase II trial.[66]

Combination Trastuzumab with Hormonal Therapy in Metastatic Breast Cancer

HER2- and HR-positive metastatic BC patients were randomised to either anastrozole alone and anastrozole plus trastuzumab. Both ORR and TTP were better in the combination arm.[67] The TanDem study is a randomised phase III clinical trial in which post-menopausal women with HER-2 node-positive MBC received treatment with anastrozole or anastrazole plus trastuzumab until disease progression. Median PFS was 4.8 months in the combination arm and 2.4 months in the anastrozole alone arm. ORR was 20.6% in the combination arm versus 6.8% with anastrazole alone. Median survival was 28.5 months with combination therapy and 23.9 months with monotherapy.[67]

Anti-angiogenesis

The addition of bevacizumab, a monoclonal antibody to vascular endothelial growth factor, to chemotherapy was tested in a randomised phase III trial, ECOG E2100, which compared bevacizumab + weekly paclitaxel versus paclitaxel alone for MBC. Seven hundred and twenty-two patients received either 90mg/m^2 of paclitaxel weekly either alone or with bevacizumab 10mg/kg or 15mg/m^2 on days one and 15. The combination arm significantly prolonged PFS compared with paclitaxel alone (median 11.8 versus 5.9 months) and increased the objective response rate (36.9 versus 21.2%). There was no significant difference in overall survival rate between the two groups (median 26.7 versus 25.2 months).[68,69] Bevacizumab, combined with taxol, has recently received approval for MBC based on this trial. Other new anti-angiogenic compounds are being developed and undergoing clinical trials. www.clinicaltrials.com[30] also evaluated agents.

Radiation Therapy

In patients with widespread metastases, specific complications and painful bone metastases may require local and directed therapy. Painful lesions in bone and CNS lesions are treated with corticosteroids followed by radiation therapy. Patients with resectable brain metastasis are offered radiation therapy after resection.[70] A small percentage of patients with isolated sites of metastases treated with locally directed therapy may remain disease free for long periods of time.

Surgery in Patients with Metastatic Breast Cancer

Surgery, with radiation, may be necessary to treat a locally ulcerated recurrence to improve the quality of life of patients. Mastectomy, as part of the management of MBC, has been shown in several retrospective studies to be advantageous in controlling local disease and improving survival.[71,72] Recent studies have looked at breast stem cells as a potential therapeutic target.[74] Removing the primary tumour may reduce further and continuous seeding with breast stem cells of metastatic properties. In the absence of prospective randomised trials, patients with single-site or oligometastases who are responding to systemic therapy are considered candidates for mastectomy. Patients with resectable single brain metastasis are best managed by surgery followed by radiation therapy.[71]

Bisphosphonates

Bisphosphonate therapy should be considered for patients with bone metastases. Randomised trials have confirmed the value of pamidronate in decreasing skeletal complications.[75] Zoledronate, a newer bisphosphonate, showed superiority to pamidronate for reducing skeletal complications with fewer adverse effects and easier administration. Bisphosphonates are recommended for patients with bone metastases on plain radiographs.[77]

Multidisciplinary Approach in Metastatic Breast Cancer

Tailoring therapy for patients with MBC has become very complex and includes multimodality therapy. It is best achieved by multi-disciplinary teams. All physicians and hospitals treating BC should have multidisciplinary tumour board conferences and, ultimately, breast units.[78] ■

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