New Strategies for Managing Metastatic Breast Cancer

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By Julie J. Olin, MD [2] and Hyman B. Muss, MD [3]

In 1999, metastatic breast cancer claimed the lives of almost 45,000 women. For the vast majority of patients, metastatic breast cancer is an incurable disease with a median survival of only 2 to 3 years after diagnosis. The

Introduction

Metastatic breast cancer is a devastating problem, with only a small percentage of patients surviving 5 years or longer. In 1999, about 45,000 women died of metastatic breast cancer—a mortality statistic that has not changed appreciably in decades. The median survival after the detection of distant metastases is about 3 years for all patients and about 2 years for patients whose disease is endocrine refractory. Thus, metastatic breast cancer remains an essentially incurable disease.

Until recently, little progress had been made in treatment. However, the development of newer endocrine, chemotherapeutic, and, most recently, biological agents, may lead to modest but definite improvements in these grim statistics. Except for clinical trials that use high-dose therapies, palliation remains the major goal of therapy.

Nevertheless, several highly debated, controversial treatment-related issues remain. These include: (1) whether initial treatment should consist of endocrine therapy or chemotherapy; (2) whether combination chemotherapy (polychemotherapy) is superior to single-agent chemotherapy; (3) the optimal sequence of administration of chemotherapeutic agents and regimens; (4) whether dose intensification is superior to standard-dose treatment; and (5) what constitutes the optimal duration of treatment.

Goals of Therapy

The most important therapeutic issue is whether treatment is being initiated with curative or palliative intent. Despite the aggressive trimodality efforts of medical oncology, radiation oncology, and surgical oncology, almost all patients with metastatic breast cancer eventually succumb to the disease. Physicians and patients should discuss and clarify the intent of treatment and decide how they wish to navigate the delicate balance among relief of symptoms, prolongation of survival, and toxicity.

An awareness of the natural history of untreated breast cancer is also important. In a series of 250 patients with breast cancer who opted for no treatment at diagnosis, median survival was 2.7 years, and 10% of patients lived 10 years or longer.[1] These data indicate that, in a small percentage of patients, breast cancer may behave as a chronic disease, even without treatment.

Prolonged remissions have been well documented in patients treated with endocrine therapy. In one study of 156 patients treated with tamoxifen (Nolvadex) for estrogen receptor-positive metastatic breast cancer, 15% were alive and 7.6% were progression free after 5 years.[2] The potential for cure using state-of-the-art polychemotherapy is well illustrated by a review of 1,581 patients with metastatic breast cancer treated between 1973 and 1982 with a doxorubicin-containing induction regimen followed by cyclophosphamide, methotrexate, and fluorouracil (CMF) maintenance therapy.[3] Complete responses occurred in 16.6% of patients, but only 3.1% remained in complete remission for more than 5 years. With a median follow-up of 16 years, only 1.6% (26 of the 1,581 initial patients) were still alive and disease free. Favorable characteristics of these remarkable long-term survivors included younger age, premenopausal status, good performance status, and a low tumor burden at the time of treatment. These sobering statistics are characteristic of the results of current chemotherapeutic regimens used in the metastatic setting.

First-Line Therapy: Hormones or Chemotherapy?
Is it better to initiate treatment with endocrine therapy or chemotherapy? Two randomized trials have addressed this question. In the first trial, 339 postmenopausal women with metastatic breast cancer, 75% of whom had unknown hormone receptor status, were randomized to receive tamoxifen alone, tamoxifen and concurrent cyclophosphamide and Adriamycin (CA), or CA alone. Although the response rates ranged from 51% in patients treated with tamoxifen plus CA to 22% in those given tamoxifen alone, overall survival rates were virtually identical among the three groups. Of the tamoxifen treated patients, 35% responded to CA as a second-line therapy.[4] In no subgroup was initial chemotherapy associated with superior survival when compared with endocrine therapy. A similar trial compared initial therapy with CMF vs tamoxifen in patients 65 years of age and older. Complete and partial response rates were 45% for patients treated with tamoxifen and 38% for those given CMF, with median response durations of 10.4 and 7.9 months, respectively. Overall survival data favored tamoxifen as initial therapy, even in estrogen receptor-negative patients.[5]

**Current Recommendations**

Currently, most patients with receptor-positive invasive breast cancer receive systemic therapy with tamoxifen at the time of initial diagnosis, and it is uncertain as to whether such patients may do as well with initial endocrine therapy in the metastatic setting. In our view, patients who relapse within 1 to 2 years after the initiation of adjuvant tamoxifen or oophorectomy are more likely to benefit from chemotherapy than from further endocrine therapy, but this decision is unlikely to have any major effect on survival. In all other patients, with the exception of patients with rapidly progressive visceral metastatic disease, initial treatment in the metastatic setting should consist of endocrine therapy. In patients who are receptor positive and seriously ill, chemotherapy combined with endocrine therapy is a reasonable option so as to maximize the patient’s chance for a rapid response. Numerous trials comparing concurrent chemotherapy and endocrine therapy with chemotherapy alone have failed to show a survival benefit for combined treatment.[6]

**Strategies for Endocrine Therapy**

Endocrine therapies should be continued indefinitely in patients with stable disease and until disease progression in responding patients. Individuals who have displayed stable disease for 4 to 6 months or longer should be observed for a withdrawal response at the time of disease progression and prior to initiation of further therapies. Agents that should be considered for hormonal therapy are described below.

**Selective Estrogen Receptor Modulators**

There is major interest in the development of new selective estrogen receptor modulators (SERMs). Tamoxifen, the first SERM widely available for the treatment of breast cancer, has demonstrated efficacy in both the metastatic and adjuvant settings and has served as the prototype for the development of newer SERMs.[7]

The search for the ideal SERM continues. This agent should have estrogen antagonistic effects on breast and endometrial tissues (less breast and endometrial cancer), estrogen agonistic effects on the hypothalamus (cessation or decrease in vasomotor symptoms), skeleton (maintenance of bone density), and liver (lowering of cholesterol), and no effect on the coagulation system. To date, no agent has met all of these goals.

Toremifene (Fareston) is currently available for the treatment of metastatic breast cancer and appears to have less estrogen agonistic effects on the endometrium compared with tamoxifen. In the metastatic setting, toremifene offers no advantages over tamoxifen.[8]

Raloxifene (Evista) has been approved by the Food and Drug Administration (FDA) for the treatment of osteoporosis in postmenopausal women and may decrease the risk of breast cancer.[9] Although raloxifene has shown activity in patients with metastatic breast cancer, no trials have directly compared it with tamoxifen or other hormonal agents. As a result, raloxifene should not be used in patients with metastatic breast cancer outside of a clinical trial. Other SERMs, including droloxifene[10] and idoxifene,[11] are unlikely to be associated with a better therapeutic index than available agents. Newer SERMs with potentially superior therapeutic indices are currently in clinical trials.

**Pure Antiestrogens**

Unlike SERMs, pure antiestrogens bind to estrogen receptors and prevent dimerization of receptors, receptor binding to DNA, and gene transcription. Fulvestrant (Faslodex), one of the first of these compounds, was studied in 19 tamoxifen-resistant patients with metastatic breast cancer.[12] Seven patients (37%) achieved partial responses lasting 3 to 20 months and six (32%) had stable disease.
lasting 9 to 23+ months. Clinical trials comparing fulvestrant with the aromatase inhibitor anastrozole (Arimidex) have recently been completed, and data should be available shortly. Other pure antiestrogens are currently being evaluated.

**Luteinizing Hormone-Releasing Hormone Agonists**

Luteinizing hormone-releasing hormone (LHRH) agonists provide a reversible method of ovarian ablation and have been shown to be as effective as surgical or radiation-induced oophorectomy in premenopausal patients with metastatic breast cancer.[13] With the goal of achieving total estrogen ablation, the addition of a LHRH agonist to tamoxifen has produced better response rates than tamoxifen alone.[14] Early results of an ongoing, three-arm, randomized trial comparing tamoxifen alone, buserelin (Suprefact) alone, and the combination of the two drugs showed that the combination regimen was associated with superior responses.[15]

Jonat et al compared the LHRH agonist goserelin (Zoladex) with goserelin and tamoxifen in 318 premenopausal and perimenopausal women with metastatic breast cancer.[16] Response rates (38% with goserelin-tamoxifen vs 31% with goserelin alone) and survival (140 vs 127 weeks) were similar, but there was a slight, but significant, improvement in time to progression favoring the combination regimen (28 vs 23 weeks). Of the 140 patients in this trial with bone metastases only, there was a significant benefit favoring those who received goserelin-tamoxifen, with respect to response, time to progression, and survival. These data suggest that the combination of an LHRH agonist and tamoxifen may be superior to single-agent treatment with either of these agents, although survival benefits are likely to be small.

**Aromatase Inhibitors**

Aromatase (estrogen synthase), an enzyme present in fat, liver, breast tissue stroma, and perhaps breast cancer cells, catalyzes the conversion of androstenedione to estrone and is responsible for estrogen synthesis in post menopausal women. Surgical and medical adrenalectomy has proved to be a successful method of endocrine treatment for metastatic disease in postmenopausal women. Older aromatase inhibitors, exemplified by ketoconazole (Nizoral) and aminoglutethimide (Cytadren), were frequently associated with substantial toxicity. New aromatase inhibitors cause little or no inhibition of glucocorticoid synthesis and obviate the need for glucocorticoid replacement.

Two types of aromatase inhibitors are currently available. The first type, which causes noncompetitive inhibition of the aromatase cytochrome P450 site, includes formestane (Lentaron) and exemestane (Aromasin). The second type includes the nonsteroidal triazole analogs anastrozole, letrozole (Femara), fadrozole, and vorozole (Rizivor), which produce competitive inhibition of the enzymatic flavoprotein site. Although the triazole inhibitors markedly suppress estradiol levels in postmenopausal women within several days of their administration,[17] they are not as effective in premenopausal women because of the very high level of estradiol synthesis in their ovaries. Several large randomized trials have compared the newer aromatase inhibitors with megestrol acetate (Table 1).[18-20] A 15% to 25% response rate (complete and partial responses) to aromatase therapy was noted in patients who showed tumor progression while receiving tamoxifen. Although therapy with various aromatase inhibitors produces responses that are similar or only slightly superior to those achieved with megestrol, aromatase therapy is associated with fewer side effects. These trials have also confirmed a clinical benefit of aromatase inhibition among patients who have had stable disease for more than 6 months. These patients did as well as those who achieved complete and partial responses.

From the perspective of both the patient and the treating oncologist, a well-tolerated therapy that is able to halt disease progression for 6 or more months is of major value. The currently available triazole aromatase inhibitors appear to be similar in efficacy and are now the therapy of choice in postmenopausal receptor-positive women who have developed metastases while receiving adjuvant tamoxifen or who experience progression of metastatic breast cancer during tamoxifen therapy.

**Strategies for Chemotherapy**

**Polychemotherapy vs Monotherapy**

Combination chemotherapy has been a mainstay of oncologic care since its introduction in the 1960s. Prior to the advent of the taxanes, most combination chemotherapy regimens for metastatic breast cancer centered around alkylating agents, such as cyclophosphamide (Cytoxan, Neosar), antimetabolites, such as fluorouracil and methotrexate, and anthracyclines, such as doxorubicin. A meta-analysis of approximately 2 decades of randomized, controlled trials evaluating cytotoxic therapies for metastatic breast cancer came to the following conclusions[21]:
1. Polychemotherapy, in general, yields higher response rates but greater toxicities than monotherapy (hazard ratio of response to polychemotherapy vs monotherapy, 0.82).

2. Polychemotherapy with anthracyclines is superior to polychemotherapy without anthracyclines.

3. Although the delivery of chemotherapeutic regimens at higher doses or for more prolonged periods produces higher response rates compared to less intensive regimens, their impact on overall survival is slight.

This meta-analysis did not include newer agents, such as the taxanes. In addition, the higher doses of chemotherapy cited in the meta-analysis would be considered standard-dose therapy today. The disappointing survival results seen with polychemotherapy, coupled with the availability of newer chemotherapeutic agents, has resulted in a reassessment of the classic dogma of treating metastatic breast cancer with combination chemotherapy. When the emphasis was shifted to quality of life (QOL) and progression-free and overall survival rather than response rates, sequential single-agent chemotherapy emerged as a major treatment strategy in the 1990s. This strategy is well supported by three recent studies: a Finnish study evaluating single-agent therapy vs combination chemotherapy as both first- and second-line treatment, an American study employing doxorubicin or paclitaxel (Taxol) alone or in combination, and an Australian study of classic CMF and prednisone vs single-agent paclitaxel.

In a Finnish study of 303 patients with previously untreated metastatic breast cancer, monotherapy with epirubicin (Ellence) followed by mitomycin (Mutamycin) was compared with cyclophosphamide, epirubicin, and fluorouracil (CEF) followed by mitomycin and vinblastine.[22] Single-agent therapy was associated with a better QOL, less toxicity, and no compromise in survival. Median survival was 18 months in patients treated with combination chemotherapy and 16 months in those given single-agent sequential therapy.

The combination of doxorubicin and paclitaxel has been extensively investigated using a variety of treatment schedules and doses. A 1998 study reported a response rate of 94% in previously untreated patients with metastatic breast cancer who were given doxorubicin (60 mg/m²) followed by a 3-hour infusion of paclitaxel (200 mg/m²) every 3 weeks for six to eight cycles.[23] This initial report spurred the Eastern Cooperative Oncology Group (ECOG) to embark on a randomized, phase III trial of doxorubicin vs paclitaxel vs the combination of doxorubicin and paclitaxel in the metastatic setting. In 739 previously untreated patients, doxorubicin (60 mg/m²) was compared to paclitaxel (175 mg/m²) followed by doxorubicin (50 mg/m²) followed 4 hours later by paclitaxel (150 mg/m²) via a 24-hour infusion) with granulocyte colony-stimulating factor (G-CSF [Neupogen]) support. Although the overall response rate in the combination therapy group was significantly higher than the response rates seen in either of the single-agent groups (47% vs 35%) and the time to treatment failure was approximately 2 months longer, overall survival was almost identical (18.9 months in the doxorubicin group, 22.2 months in the paclitaxel group, and 22.0 months in the combination therapy group).[24]

In an Australian study, 209 patients with previously untreated metastatic breast cancer were randomized to receive paclitaxel (200 mg/m² over 3 hours every 3 weeks) for eight cycles vs CMFP (cyclophosphamide, methotrexate, fluorouracil, and prednisone) for six cycles, with epirubicin recommended as second-line therapy.[25] Although QOL assessments were similar in both treatment arms, single-agent paclitaxel was associated with significantly less myelosuppression, mucositis, and infection. Median survival in the CMFP-treated group was significantly lower than that in the paclitaxel-treated group (13.9 vs 17.3 months).

**Order of Administration: First-Line vs Salvage Therapies**

Given the large number of chemotherapeutic agents available for the treatment of metastatic breast cancer, the clinician must consider several patient characteristics to help guide the order of administration of cytotoxics to maximize the chances for a favorable therapeutic index. Patient age, performance status, renal and hepatic function, disease-free interval from initial diagnosis, type of adjuvant therapy received, site(s) of metastatic disease, hormone receptor status, menopausal status, comorbid disease, and patient preferences must all be assessed prior to the initiation of chemotherapy. With the introduction of the humanized anti-HER2 monoclonal antibody trastuzumab (Herceptin), the patient's HER2 (c-erbB-2) status should also be taken into consideration. Although there is no agreed-upon, well-established flowchart or cookbook of the order of administration of chemotherapeutic agents, the guidelines listed in Table 2 may be helpful in
new strategies for managing metastatic breast cancer

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Determining first-line and subsequent salvage treatments. Newer agents worthy of consideration in the metastatic setting are described below and summarized in Table 3.

Role of New Chemotherapeutic Agents

Anthracyclines

The anthracycline family consists of doxorubicin, epirubicin, mitoxantrone (Novantrone), and the recently introduced liposomal doxorubicins. Although single-agent doxorubicin classically achieves a 40% to 50% response rate as first-line therapy and a 15% to 25% response rate as second-line therapy,[26] it has been most commonly used in combination with other agents, such as cyclophosphamide and fluorouracil. Newer doublets include doxorubicin combined with taxanes, vinorelbine (Navelbine), or gemcitabine (Gemzar). In order to further enhance the therapeutic index of doxorubicin, attempts to minimize anthracycline-induced cardiomyopathy have led to the development of dexrazoxane (Zinecard), a well-tolerated chelating cardioprotectant,[27] as well as the development of liposomal doxorubicins.

Liposomal encapsulation of doxorubicin prolongs its plasma half-life and may enhance its tumor localization while lowering its toxicity to normal tissues.[28] The side effect profile for liposomal doxorubicin, which includes mild myelosuppression, mucositis, and hand-foot syndrome (for some but not all preparations), contrasts with the alopecia, nausea and vomiting, cardiotoxicity, and more significant myelosuppression associated with traditional doxorubicin use.

As a single agent, liposomal doxorubicin Caelyx (Doxil) showed an overall response rate of 31% and a median survival of 7 months in 51 patients with previously untreated or doxorubicin-naive metastatic breast cancer.[28] A phase III trial comparing cyclophosphamide and either liposomally encapsulated doxorubicin (TLC D-99) or standard doxorubicin as first-line treatment of metastatic breast cancer demonstrated a 43% response rate in both treatment arms.[29] Median survival was 21.2 months for patients given liposomally encapsulated doxorubicin and 16.4 months for those who received standard doxorubicin. There was significantly less cardiotoxicity and grade 4 myelosuppression with the liposomally encapsulated anthracycline.

Taxanes

In addition to the era of dose intensification, the 1990s have, in many respects, been the decade of the taxanes.[30] Paclitaxel and docetaxel (Taxotere) are microtubule stabilizers that prevent reorganization of the microtubular skeleton, with resultant cell-cycle growth arrest. Paclitaxel may also be a potent inhibitor of tumor-induced endothelial cell angiogenesis[30] and apoptosis.

Paclitaxel[31]After an initial report demonstrated a 57% response rate to paclitaxel in previously untreated patients with metastatic breast cancer,[31] many trials were conducted to address the optimal dosing and scheduling of this agent. Single-agent paclitaxel has been studied in low and high doses, as a short vs long infusion, and using a weekly vs triweekly administration schedule.[30] Several randomized trials of paclitaxel administered at 135, 175, 210, or 250 mg/m² using a 3-hour infusion found no significant differences in response rates or survival.[32] In an attempt to enhance cytotoxicity through prolonged tumor exposure, several trials have evaluated the administration of paclitaxel via 24- or 96-hour continuous infusions. Although higher response rates have been seen with infusion durations longer than 3 hours, the lack of a significant survival benefit and the increased myelosuppression demonstrated in most studies have argued against the added inconvenience and expense of prolonged infusion therapy.[32] Another method of extended cumulative chemotherapeutic exposure involves dose-dense therapy with weekly 1-hour paclitaxel. In a Memorial Sloan-Kettering Cancer Center study of 30 patients with taxane-naïve metastatic breast cancer, weekly paclitaxel was administered at a dose of 100 mg/m² over 1 hour until disease progression. At a median delivered dose intensity of 91 mg/m²/wk, an overall response rate of 53% with a median duration of 7.5 months was observed, even in anthracycline-resistant patients. Minimal myelosuppression was encountered, although grade 3 sensorimotor neuropathy developed in 24% of patients.[33] An ongoing Cancer and Leukemia Group B randomized trial (CALGB 9840) is comparing 175 mg/m² of paclitaxel infused over 3 hours every 3 weeks with 100 mg/m²/wk of paclitaxel for 6 weeks followed by 80 mg/m²/wk. At present, a dose of 175 mg/m² over 3 hours every 3 weeks should be considered standard treatment.

Paclitaxel has been combined in doublets with multiple agents, including doxorubicin, epirubicin, carboplatin (Paraplatin) and cisplatin (Platinol), cyclophosphamide, fluorouracil with and without leucovorin (Wellcovorin), and vinorelbine. Relatively high response rates have been noted with some of these regimens, but no clear-cut survival advantage of combination regimens over single-agent
Docetaxel has been shown.\[32\].

**Docetaxel**
The combined results of several phase II trials using doce-taxel (100 mg/m² every 3 weeks) in patients with previously untreated metastatic breast cancer showed an overall response rates of 61% with a median survival of 16 months.\[34\] Docetaxel also has significant activity in previously treated patients, including those who have been exposed to or demonstrated resistance to alkylators, anthracyclines, or paclitaxel. The pooled results of three phase II trials using docetaxel in patients with anthracycline-resistant metastatic breast cancer revealed an overall response rate of 41% with a median survival of 10 months.\[35\] In a phase II trial of docetaxel in patients with paclitaxel-resistant metastatic breast cancer, an 18% overall response rate was seen with a 10-month median survival.\[36\] Weekly docetaxel, at a dose of 35 to 45 mg/m², has been associated with response rates of 40% to 50% in patients with previously treated metastatic breast cancer.\[37,38\] Like paclitaxel, this dose-dense weekly schedule of docetaxel produced less myelosuppression.

Docetaxel has been compared to doxorubicin and to the combination of mitomycin and vinblastine in two large phase III trials. In the first trial involving 326 patients with prior alkylating agent exposure, docetaxel (100 mg/m²) was compared to doxorubicin (75 mg/m²), with each agent administered every 3 weeks for up to seven cycles. The median survival for both groups was 15 months, but the 48% response rate with docetaxel was significantly higher than the 33% rate with doxorubicin. Febrile neutropenic episodes, cardiotoxicity, stomatitis, and nausea and vomiting were seen more frequently in doxorubicin-treated patients, while neuropathy, fluid retention, and diarrhea were more common in docetaxel-treated patients.\[39\]

In the second phase III trial, docetaxel outperformed combination mitomycin and vinblastine with respect to both overall response rate (30% vs 11%) and survival (median, 11.4 vs 8.7 months).\[40\] Docetaxel has combined with both doxorubicin and epirubicin, as well as doxorubicin and cyclophosphamide. Impressive response rates of 70% to 80% have been noted for these combination regimens. Although grade 4 neutropenia was commonly seen in these trials, only a few febrile neutropenic episodes occurred and cardiac function was well preserved.\[41\]

**Vinorelbine**
Vinorelbine, a semisynthetic vinca alkaloid that inhibits nonaxonal microtubule assembly, has demonstrated response rates and median survivals similar to those obtained with both doxorubicin and paclitaxel.\[26\] Vinorelbine's role as single-agent salvage therapy in both anthracycline- and taxane-resistant metastatic breast cancer was explored in a dose-intensification study of vinorelbine administered at 35 mg/m²/wk with G-CSF support. Although an overall response of 25% was seen in this heavily pretreated population, prohibitive myelosuppression and neuropathy were also encountered.\[42\]

Vinorelbine has been coupled with an anthracycline, fluorouracil, melphalan (Alkeran), mitomycin, and paclitaxel for use as both first- and second-line therapy in metastatic breast cancer. The largest first-line doublet trial evaluated 89 patients who were given vinorelbine (25 mg/m² on days 1 and 8) and doxorubicin (50 mg/m² on day 1) on an every-3-week cycle. The overall response rate was 74% with a median survival of 27.5 months. Serious side effects included a 16% rate of neutropenic febrile episodes and significant cardiotoxicity in 10% of patients who had previously received adjuvant doxorubicin.\[43\]

**Gemcitabine**
Gemcitabine is a nucleoside analog that interrupts DNA synthesis via ribonucleotide reductase inhibition and DNA chain termination.\[44\] In a phase II trial of 44 patients with advanced breast cancer, half of whom had received prior chemotherapy for metastatic breast cancer, single-agent gemcitabine was administered at 800 mg/m²/wk for 3 consecutive weeks in a 4-week cycle. With a mean number of 2.7 cycles administered, a response rate of 25% and a median survival of 11.5 months were achieved.\[44\] Mild hematologic toxicity was seen, with only one episode of documented infection. Additional trials of gemcitabine coupled with anthracyclines, taxanes, and other agents are underway.

**Capecitabine**
Capecitabine (Xeloda) is an orally administered fluoropyrimidine prodrug that undergoes a three-step metabolism to finally produce fluorouracil. The last step in this conversion is catalyzed by thymidine phosphorylase, an enzyme that is preferentially expressed in several human cancers and, thus, may result in a higher therapeutic index for capecitabine as compared to fluorouracil.\[45\] Capecitabine's role as a remarkably active and well-tolerated salvage therapy for anthracycline and taxane-resistant metastatic breast cancer has been demonstrated in a multi-institutional phase II trial. Heavily treated patients (162) with a median age of 56 years received capecitabine (2,500...
mg/m²/d in divided doses) for 2 weeks followed by a 1-week rest period. All patients had previously received paclitaxel; 91%, anthracycline therapy; and 82%, a fluorouracil-containing regimen. The overall response rate was 20%, with an additional 40% of patients displaying stable disease for a median of 3.5 months; median survival was 12.8 months. The most common grade 3 and 4 treatment-related side effects included hand-foot syndrome (grade 3 in 10% of patients), diarrhea (grade 3 in 11% and grade 4 in 3%), and fatigue (grade 3 in 7%). Remarkably, little myelosuppression was experienced, despite the study population's extensive prior chemotherapy exposure. No significant alopecia occurred.[45]

Capecitabine's role as initial therapy for metastatic breast cancer has yet to be defined. In a small, randomized, phase II trial comparing capecitabine with CMF as first-line treatment of metastatic breast cancer in patients over the age of 55 years, the response rate was 25% with capecitabine (including eight complete responses) and 16% with CMF (no complete responses). Grade 3 and 4 treatment-related side effects of hand-foot syndrome and diarrhea were reported by 44% of patients receiving capecitabine and 20% of patients receiving CMF.[46] Equal efficacy was also noted in a small, randomized, phase II trial comparing capecitabine and paclitaxel.[47]

In addition, other new oral fluoro-uracil analogs, including UFT (uracil and tegafur) and fluorouracil/eniluracil, are undergoing evaluation in metastatic breast cancer and may hold promise.[48]

Chemotherapy Dose Intensification

The concept of dose intensification, as introduced in the mid-1980s,[49] has dominated the chemotherapeutic approach in advanced breast cancer in both the high-risk adjuvant and metastatic settings. With the advent of hematopoietic growth factor support and improved stem-cell collection methods, a multitude of studies on dose intensification have been reported. Of note, many studies of dose-intensive therapy requiring growth factor support have failed to demonstrate significant improvements in survival, despite their increased toxicities, costs, and complexity of administration.[50]

Randomized Trials

Four randomized trials comparing high-dose chemotherapy and progenitor cell support with standard combination chemotherapy have been reported. In the French PEGASE 4 trial, 61 patients with chemosensitive metastatic breast cancer were randomized to receive high-dose cyclophosphamide, mitoxantrone, and Alkeran (CMA) vs standard-dose CMA. No significant differences in 2-year survival were found, although there was a trend in favor of high-dose CMA (median survival, 36.1 vs 15.7 months).[51] At 5 years, the median survival rate was 19% in the standard-dose arm and 30% in the high-dose arm.[52] The small number of patients in this trial limit its statistical power to detect small but clinically significant differences.

In the Duke trial of hormone-insensitive metastatic breast cancer involving three or less bony metastatic foci, 98 patients who achieved complete responses following induction therapy with Adriamycin, fluorouracil, and methotrexate (AFM) were randomized to receive either immediate high-dose chemotherapy with cyclophosphamide, cisplatin, and carmustine (BCNU), the STAMP I regimen, and autologous cellular support or observation followed by high-dose chemotherapy upon progression. Although the 0.9 year progression-free survival associated with immediate high-dose chemotherapy was significantly longer than the 0.3 year progression-free survival for the observation group, the delayed high-dose chemotherapy arm showed a surprisingly superior overall survival (3.2 vs 1.9 years).[53]

Both the PEGASE and Duke trials used induction chemotherapy to determine chemosensitivity prior to proceeding with high-dose chemotherapy. The Duke study involved only patients with limited bony metastatic disease who responded completely to induction therapy, whereas the smaller French study included patients with multiple metastatic foci, as well as both complete and partial responders to induction chemotherapy. The Duke study suggested that the timing of high-dose chemotherapy affected survival in metastatic breast cancer, although the median duration of observation in the delayed high-dose chemotherapy treatment group of only 6 months raises concerns over whether the two groups were truly distinct from one another.

The third randomized trial, conducted in South Africa, used a different approach of immediate high-dose chemotherapy without induction. This study randomized 90 untreated patients with metastatic breast cancer either to high-dose cyclophosphamide, Novantrone, and VePesid (HD-CN) for one to two cycles with stem-cell transplantation or to standard doses of cyclophosphamide, Novantrone, and vincristine (CNV). The overall response rate for high-dose CNV was 95%, with 51%
of patients achieving complete responses, as compared with an overall response rate of 53% for standard-dose CNV, with only 4% complete responses. Significant improvements in favor of high-dose CNV were seen with respect to both median response duration (80 vs 34 weeks) and median survival (90 vs 45 weeks).[54]

A recent update of this trial revealed that nine patients who received high-dose therapy have remained in complete response after more than 5 years.[52] Criticisms of this trial include its small sample size, the choice of CNV as standard first-line therapy, the low response rates and survival duration in the CNV arm, and the use of tamoxifen following chemotherapy only in the chemotherapy responders.

A second South African trial using the upfront dose-intensified approach adjuvantly in patients with high-risk breast cancer has recently come under extensive scrutiny. Following an on-site audit by an independent investigative team, serious scientific misconduct by the principal South African researcher was discovered.[54a] The review included medical records only of patients with high-risk breast cancer.

The fourth and largest published randomized trial, the Philadelphia intergroup study of chemo-sensitive metastatic breast cancer, randomized patients with either a complete or partial response to induction chemotherapy with high-dose cyclophosphamide, thiopeta (Thioplex), and carboplatin (the STAMP V regimen) and stem-cell support or to conventional maintenance with CMF. Of the 513 eligible participants who were initially enrolled, 303 displayed chemo-sensitive disease following four to six cycles of induction with CAF or CMF (56 complete and 247 partial responses). Although these 303 patients were eligible for randomization, only 199 were subsequently randomized, and a further 10% refused their randomized assignment.

In the final analysis, 101 patients received high-dose chemotherapy, compared with 79 patients treated with CMF maintenance. After a median follow of 31 months, no difference in survival between the two groups was detected (46% with high-dose chemotherapy vs 52% with CMF).[55] Subgroup analysis in patients who achieved a complete vs partial response also showed no significant difference in overall survival. Criticism of this trial centers on its high attrition rate and its low statistical power to detect even large potential differences among the treatment groups.[56]

**Selection Bias**

Selection bias must also be considered when evaluating the merits of high-dose chemotherapy. Patients who receive high-dose chemotherapy with stem-cell support are often highly selected for many of the same factors that may also predict response to conventional dose therapy.[57]

In a retrospective review of 1,581 patients with metastatic breast cancer treated on 18 different protocols using standard-dose doxorubicin-containing regimens, patients were grouped as potential high-dose chemotherapy transplant candidates vs nontransplant candidates. Criteria for high-dose chemotherapy candidacy included age less than 60 years, good performance status, response to induction therapy, and good marrow, hepatic, and cardiac function.

Using these criteria, the median survival for the 645 high-dose chemotherapy candidates was 30 months, as compared with 17 months for the 936 noncandidates.[58] Overall survival for this highly selected potential high-dose chemotherapy candidate group is similar to the median survival duration of 33 months noted among 680 assessable patients from the North American Bone Marrow Transplant registry treated with high-dose chemotherapy.[59]

A recent analysis compared the outcomes of patients given standard-dose chemotherapy on CALGB trials with a database of patients entered into high-dose chemotherapy trials in the North American Bone Marrow Transplant Registry. No difference in survival was noted, even after extensive subset analysis.[60]

Thus, at this point, high-dose chemotherapy should still be considered a research approach.

**Duration of Systemic Therapy**

**Endocrine Therapy**

What is the optimal duration of systemic therapy in the metastatic setting? Endocrine therapies should be continued until disease progression. In patients with measurable lesions (ie, skin, lymph node, lung, and liver metastases), responses to endocrine therapy and chemotherapy are generally seen within 4 to 12 weeks.[2] Responses in bony metastatic disease are hard to measure during the first 3 months of treatment, and improvement in bone pain, when initially present, may be the earliest clue to treatment success.[61]

Flare reactions, characterized by increasing bone pain, worsening of skin lesions, and/or a rise in serum chemistries and tumor markers (eg, calcium, alkaline phosphatase, and CA 15-3), can occur
within several days to several weeks of treatment with either endocrine therapy or chemotherapy and can be confused with disease progression. Clinicians who suspect a tumor flare should treat patients symptomatically and wait to see whether they demonstrate any improvement.\[62,63\]

**Chemotherapy**

The optimal duration of chemotherapy for metastatic breast cancer remains controversial. Several randomized studies have attempted to determine whether induction chemotherapy should be followed by prolonged maintenance therapy, or whether the patient should be monitored after induction, with chemotherapy reinitiated upon disease progression. These randomized trials are concisely summarized by Miller and Sledge.\[57\]

Although several studies have shown an improvement in time to disease progression with maintenance therapy, no overall survival benefit was associated with prolonged therapy. Two trials included QOL assessments and surprisingly showed higher QOL in continuously treated patients; other studies without QOL assessments emphasized tolerable although additional treatment-related toxicities due to maintenance therapy.\[64\].

Patients who desire a drug holiday after four to six cycles of induction therapy can be reassured that they will not be compromising their survival but that they are likely to have a shorter initial remission duration than if they continue treatment. Newer trials are studying the use of biological agents and antiangiogenesis agents in patients with metastatic breast cancer who have responsive or stable disease after four to six courses of induction therapy.

**Biological Agents**

Trastuzumab

Overexpression of p185\(^{\text{HER2}}\), a transmembrane glycoprotein receptor encoded by the HER2 gene, occurs in 25% to 30% of breast cancers and confers a poorer prognosis.\[65\] The recombinant humanized monoclonal antibody trastuzumab binds specifically to the extracellular domain of p185\(^{\text{HER2}}\), with resultant inhibition of growth of HER2-overexpressing tumors. This antibody was recently approved by the Food and Drug Administration (FDA) for use in patients with metastatic breast cancer.

In a multinational study of 222 women with HER2-overexpressing metastatic breast cancer who had received previous chemotherapy (94% anthracyclines, 67% taxanes, and 26% high-dose chemotherapy and stem-cell support), trastuzumab was administered as a 4-mg/kg loading dose followed by a 2-mg/kg weekly maintenance infusion. The response rate was 15% (8 complete and 26 partial responses) with a median response duration of 9.1 months; median survival for all patients was 13 months.

The most common adverse event occurred during administration of the loading dose and included mild pain, fever, chills, and nausea in 40% of patients. Cardiac dysfunction occurred in 4.7% of patients, almost all of whom had received prior anthracycline therapy.\[66\]

A multinational, randomized, phase III trial evaluated the efficacy and safety of trastuzumab as first-line therapy in combination with either an anthracycline plus cyclophosphamide or single-agent paclitaxel in patients with HER2-overexpressing metastatic breast cancer. Patients who had received adjuvant anthracyline chemotherapy were randomized to paclitaxel (175 mg/m\(^2\) over 3 hours every 3 weeks) with or without trastuzumab. Patients without prior anthracycline exposure were randomized to doxorubicin (60 mg/m\(^2\) ) or epirubicin (75 mg/m\(^2\)) and cyclophosphamide (600 mg/m\(^2\)) every 3 weeks with or without trastuzumab.

Overall response rates (49% vs 32%) and time to progression (7.6 months vs 4.6 months) were significantly higher in the 235 patients who received chemotherapy and trastuzumab than in the 234 patients who received chemotherapy alone.\[67\] A recent update of this trial after a 25-month median follow-up showed a significant survival advantage (25.4 vs 20.9 months) for trastuzumab-treated patients.\[68\]

Asymptomatic and symptomatic cardiac dysfunction occurred in 9% of patients treated with an anthracycline alone and 39% of patients treated with an anthracycline plus trastuzumab. Cardiac dysfunction was reported in 2% of the paclitaxel-treated patients, as compared with 12% of the paclitaxel- and trastuzumab-treated patients.\[67\] The mechanism of this cardiotoxicity is currently unknown. Trastuzumab should be used with caution in patients with cardiac dysfunction or patients who have recently completed anthracycline-containing chemotherapy.

**Antiangiogenesis Agents**

Multiple strategies for therapeutic angiosuppression are presently under development. Angiogenic inhibitors currently in clinical trials for metastatic breast cancer include the matrix metalloproteinase...
inhibitors, such as marmistat; endothelial cell proliferative inhibitors, such as endostatin; angiogenic growth factor inhibitors, such as anti[vascular endothelial growth factor (VEGF) monoclonal antibody and thalidomide (Thalomid); and copper chelators, such as tetrathiomolybdate.[69]. Current trials involve single-agent angiogenic inhibitors in addition to combinations of angiogenic inhibitors to induce [panstasis,] or the coupling of angiogenic suppressors with various established chemotherapeutic agents.

**Supportive Care**

Significant advances in supportive care that have improved QOL in the metastatic setting include the use of epoetin alfa (erythropoietin [Epogen, Procrit]) for cancer-related fatigue and bisphosphonates for bone metastases.

**Epoetin Alfa**

Cancer-related fatigue is often a prominent and distressing symptom. Of the many possible physiologic and psychologic factors causing fatigue, anemia has been targeted as a potentially treatable cause.

Two large trials involving approximately 2,800 patients who were receiving chemotherapy for a variety of nonmyeloid malignancies tested epoetin alfa at doses of 150 to 300 U/kg or 10,000 to 20,000 U administered three times weekly for 4 months. Hemoglobin increased roughly 2 mg/dL over the course of epoetin alfa therapy and red blood cell transfusions were significantly reduced. Quality-of-life measurements of energy and activity levels and overall well-being improved approximately 10%, as measured on a visual analog scale.[70] Prospectively collected tumor response data in one of these trials showed that the improvements in QOL parameters were associated with epoetin use and were independent of tumor response.[71]

**Bisphosphonates**

As the most common site of disseminated disease in breast cancer, bony metastases may result in excessive pain, pathologic fractures, spinal cord compression, and hypercalcemia. Bisphosphonates, as exemplified by pamidronate (Aredia), are pyrophosphate analogs that bind tightly to bony hydroxyapatite to limit bone resorption.[72] Pamidronate has been shown to provide significant palliative benefit in patients with osteolytic metastatic foci.

Hortobagyi et al randomized 382 women with metastatic breast cancer and bony lytic disease undergoing chemotherapy to 2 years of therapy with either pamidronate (90 mg intravenously every 3 to 4 weeks) or placebo. Overall survival was similar in the two groups, but the pamidronate-treated group experienced significantly decreases in skeletal complications, including pathologic fractures, the need for radiation therapy, and hypercalcemia. The median time to the first skeletal complication was 13.9 months in the pamidronate-treated group vs 7 months in the placebo group. Although pain scores and analgesic use increased over time in both treatment groups, the increases were significantly higher in the placebo group.[73]

Theriault et al used an almost identical study design to assess the value of pamidronate in patients treated with hormonal therapy, and noted similar findings. The median time to the first skeletal complication was 10.4 months in the pamidronate-treated group and 6.9 months for patients who placebo.[74] Pamidronate has few side effects, with fever and chills being the most common. Controversy exists regarding when to initiate bisphosphonate therapy, given its lengthy infusion time and overall cost. Randomized trials seem to favor pamidronate use when lytic metastases are first discovered.[72] The duration of bisphosphonate therapy, especially in patients who experience progression of skeletal metastases while receiving bisphosphonate treatment, and its use in osteoblastic metastases have not yet been addressed in clinical trials. Newer agents under study, such as zoledronate, are more potent than pamidronate and require less infusion time.

**Conclusions**

The best treatment option for patients with metastatic breast cancer is enrollment in a clinical trial. This is especially true for treatment programs using dose-intensified regimens. Outside of a clinical trial, we favor the strategies listed in Table 1. With standard treatment, whether endocrine therapy or chemotherapy, the goal is palliation, with improvement or maintenance of the highest possible QOL.

**References:**

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