

Chapter 12
Management of advanced breast cancer

The clinical course of metastatic breast cancer is variable; this heterogeneity results in large variations in growth rate and responsiveness to systemic therapy. The heterogeneity of patients with metastatic breast cancer must be emphasized. Rarely, patients with metastatic breast cancer succumb to their disease within weeks of a diagnosis; others live with the disease for many years. Many patients have metastatic involvement that is confined to bone or soft tissue, while others have predominantly visceral disease. CNS involvement is relatively unusual as a presenting sign or symptom of metastatic disease. It is important, both in the approach to individual patients and in considering clinical trial results, to have an understanding of the variability of metastatic breast cancer. Table 10.1. outlines the clinical and laboratory characteristics of patients with metastatic breast cancer who have an indolent versus aggressive clinical course. No single factor explains the heterogeneity that is seen clinically. It is uncertain to what extent the administration of prior adjuvant therapy affects a patient's prognosis in the setting of advanced disease. There are reports of patients responding to chemotherapy in the metastatic setting even after receiving the identical therapy in the adjuvant setting. On the other hand, a patient who develops an early recurrence following treatment with an effective adjuvant regimen (i.e. CA: cyclophosphamide and Adriamycin) followed by paclitaxel followed by tamoxifen almost certainly has a relatively poor outlook in the metastatic setting.

Favorable Prognosis (<i>Indolent Clinical Course</i>)	Unfavorable Prognosis (<i>Aggressive Clinical Course</i>)
Long disease-free interval (usually considered at least 2 y from initial diagnosis)	Short disease-free interval (usually considered less than 2 y from initial diagnosis) ^a
Hormone receptor positivity	Hormone receptor negativity
Response to prior therapy	Lack of response to prior therapy
Lack of visceral involvement	Presence of visceral involvement, CNS involvement, or both
Limited sites and bulk of disease	Multiple sites of disease and extensive involvement at these sites
HER-2/neu negative	HER-2/neu positive ^b

^a. Although 2 years is often used as an arbitrary cutoff in separating early recurrences, the longer the disease-free interval, the more indolence one can expect in terms of tumor behavior.

^b. It is not clear that HER-2/neu positivity remains an adverse prognostic factor with the availability of trastuzumab.

Table 10.1. Factors that affect prognosis in patients with metastatic breast cancer

Diagnostic Workup

Patients with metastatic breast cancer have organ involvement assessed by symptoms and physical examination. A biopsy to establish metastatic disease provides an opportunity to reassess the hormone receptor status of the tumor. While few tumors evolve from ER negative to ER positive, more frequently there can be loss of hormone receptors over time. With the availability of Herceptin, the result of a HER-2/*neu* assay is often important in making treatment decisions, although this can often be assessed from specimens of the primary tumor.

Recommendations for the laboratory and radiographic evaluation of patients with newly diagnosed metastatic breast cancer have been established by the National Cancer Center Network. Routine blood work consisting of complete blood counts and liver function tests are recommended. In addition, chest radiographs and bone scans are recommended. The decision to proceed with other-radiographic studies can be based on symptoms, although many physicians obtain a baseline assessment of liver involvement with a CT scan or MRI, particularly if the presence of liver metastases would change treatment. Since intracranial involvement is extremely rare, in newly diagnosed patients in the absence of CNS symptoms, a CT or MRI of the brain is not usually recommended for a woman with a new diagnosis in the absence of symptoms. Sometimes it could be useful to realize a PET to get an overview of metastatic disease. The use of tumor markers in the management of patients with breast cancer remains controversial. It is reasonable to obtain a CA 15-3 and more accessorially carcinoembryonic antigen(CEA), and CA 27-29, level looking for an elevation in either of these proteins. If elevated, they can be followed to determine if rising or falling levels correlate with the patient's disease status. Caution should be used in changing a treatment regimen based on tumor markers alone. If tumor markers are negative at the time of diagnosis, they can be checked again when the patient has disease progression, as they are more commonly elevated in patients with more extensive disease.

Choice of Systemic Therapy

The vast majority of patients with metastatic breast cancer receive some form of systemic therapy. Hormonal therapy can be indicated only for patients with hormonal receptor positivity on the primary (or metastatic) tumor. (Patients with both estrogen and progesterone receptor positivity are more likely to respond to hormonal therapy than are those with ER-positive/PR-negative or ER-negative/PR-positive tumors). (A trial of hormonal therapy may be justified even in the presence of negative hormone receptors since a small number of patients, with ER-negative/PR-negative tumors respond to a hormonal intervention). Immunotherapy with trastuzumab (anti-HER2 antibody) can be

considered only for patients with strong expression of HER2/neu (+++) on the primary tissue or on a metastatic specimen. (Fig. 12.1).

Hormonal Treatment

Because of the limited toxicity with most hormonal therapies, patients who have hormone receptor-positive tumors and a limited to moderate disease burden should generally receive hormonal therapy. The key issues that the clinician must consider in proceeding with initial hormonal therapy are whether or not the patient is likely to respond to the treatment and whether the patient would be adversely affected if she did not respond to treatment and was started on chemotherapy 2 to 3 months later. Visceral disease, particularly low-volume and asymptomatic disease, is not a contraindication to the use of hormonal therapy; however, the patient with extensive visceral disease is probably better served by chemotherapy. If a patient with a hormone receptor-positive cancer is initially treated with chemotherapy, the clinician should consider returning to hormonal therapy at some point in the future.

Choice of drugs

It depends on the menopausal status and of the kind of the adjuvant treatment given previously to the patient. For premenopausal patient, if the patient did not receive tamoxifen this is the preferred treatment. If yes and if the interval between the end of the adjuvant treatment by tamoxifen and the diagnosis of the relapse is sufficient, it is possible to try again the administration of tamoxifen. If the patient is obviously resistant to tamoxifen, castration (chemical by LHRH agonist (Gosereli) or by radiotherapy) is to be considered, but often chemotherapy is preferred. None of the new SERMs, including idoxifene, droloxifene, and toremifene (Farestone[®]), has been found to have activity in tamoxifen-refractory patients. We have to wait for the results of randomized trials to know if Fulvestrant can be used in this case. For post menopausal patients and mainly, if the received as adjuvant treatment tamoxifen, one of the aromatase inhibitors (AI) steroidal (exemestane, formestane) and non-steroidal (anastrozole, letrozole) is indicated. In case of resistance it is possible to shift to another AI, steroidal if the patient received initially a non steroidal AI and reciprocally. If the patient received an AI as adjuvant treatment, tamoxifen as first line of treatment of metastatic disease is indicated.

Here also, we have to wait for the results of two large prospective randomized trials comparing Fulvestrant to anastrozole in tamoxifen-refractory patients, and to tamoxifen in patients who have never received tamoxifen or not received the drug for at least one year. Fardazole is being less potent and less specific, and formestane is less convenient and equivalent to tamoxifen and megestrol. ???

The semisynthetic progestins: medroxyprogesterone acetate and megestrol acetate are the two most active agents of this class of hormones available for treating breast cancer patients and can be used as a third or fourth line of hormonal therapy.

In routine there is no place for combination Endocrine Therapy except if we consider the modest improvement in response rate, progression-free survival, and overall survival associated with the combination of LHRH-A plus tamoxifen versus LHRH-A

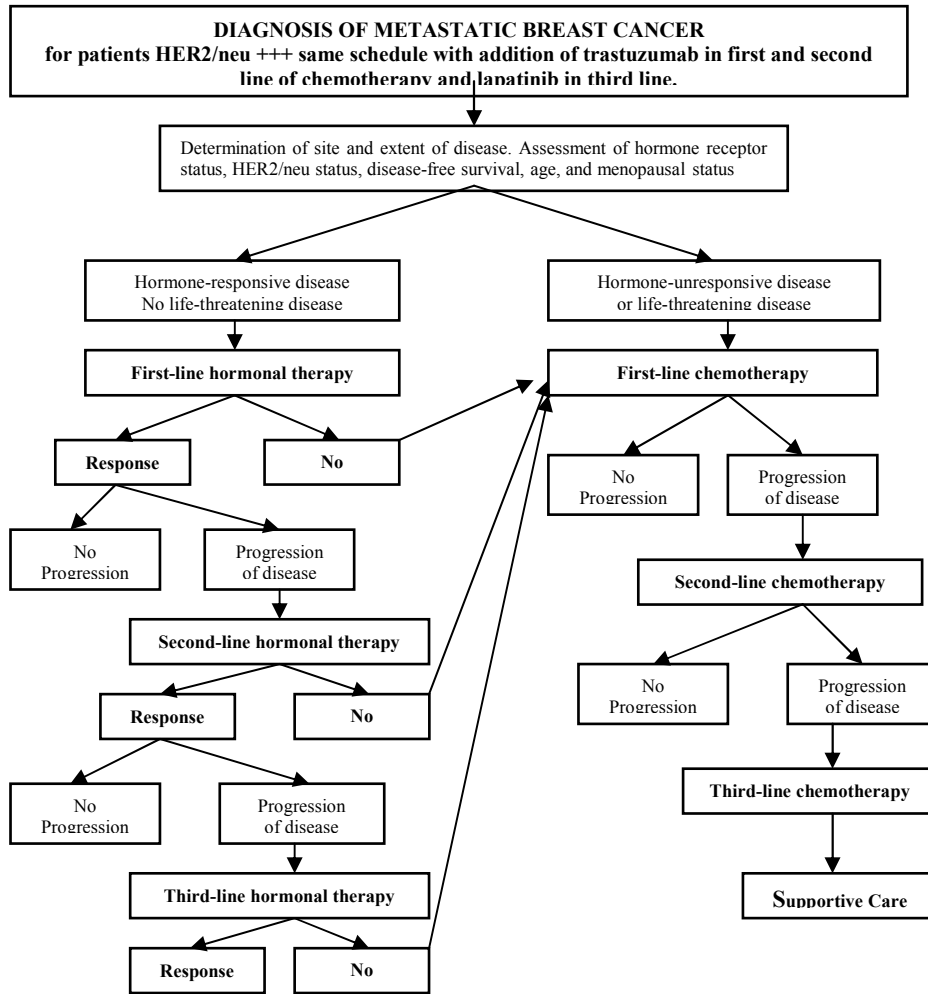


Figure 10.1. Optimal palliative therapy for women with metastatic breast cancer

Cytotoxic Chemotherapy for Metastatic Breast Cancer

Single agents

Chemotherapy is the most commonly used palliative treatment for metastatic breast cancer patients whose tumors become hormone refractory and for those patients whose tumors are expected to be hormone resistant from the start with the goal of ongoing symptomatic control and modest prolongation of survival.

A large number of chemotherapeutic agents are available to patients and their physicians: anthracyclines, alkylating agents, antimetabolites and microtubule inhibitors. Response rates for these agents range from 20% to high 60% (Table 12.2).

Drug	ORR (%) (mean)	Drug	ORR (%) (range)
Doxorubicin*	43	Methotrexate*	26
Cyclophosphamide*	36	Paclitaxel*	36-62
Fluorouracil*	28	Docetaxel*	52-68
Capecitabine **	29	Vinorelbine*	40-52
Mitoxantrone*	27		
ORR = objective response rate			
* in First-Line, ** in pretreated patients			

Table 10.2. Single-Agent Chemotherapy Treatment of Metastatic Breast Cancer

Anthracyclines are probably the more often used of chemotherapy in the treatment of breast cancer: the main drug is doxorubicin. Except the hematologic toxicity, the main side effect of this drug is the cardiac one. So some times derivated products can be used: 4-epi adriamycin. Caelyx which is doxorubicin coated with sterically stabilized liposomes and idarubicin, which has oral bioavailability. These drugs should be less toxic and, in particular, less cardiotoxic than the parent compound; their exact role in breast cancer management awaits the completion of ongoing phase III trials. There is particular interest in these drugs with regard to treatment of elderly patients and development of combinations with toxicity profiles that are more favorable than those of doxorubicin-based regimens. Mitoxantrone is “apparentée” product from antracendione family.

In the antibiotic family, we include mitomycin which has a renal limiting toxicity. Among the **alkylating agents**, the main product is cyclophosphamide.

Three antimetabolites are used: Methotrexate and Fluoro-Uracil (5FU). Capecitabine, belongs to the subfamily of 5-FU prodrugs, which have acceptable oral bioavailability and produce results somewhat similar to those of active but inconvenient prolonged 5-FU infusion schedules. Capecitabine induced a 20% objective response rate in 162 heavily pretreated patients; a 29% response rate was documented in 42 of these patients, who had experienced rapid progression with both anthracyclines and taxanes.

Gemcitabine is the last antimetabolite showed good single agent activity as both first and second line treatment in advanced breast cancer. One of the most exciting aspects of this drug is its modest toxicity profile. This makes it particularly suitable for use as palliative therapy in elderly patients and in those with poor performance status.

Microtubules inhibitors : the discovery of the taxanes paclitaxel (Taxol) and docetaxel (Taxotere) has been the most encouraging chemotherapy development of the late 1980s and early 1990s that led to improvement of overall survival.

Docetaxel is generally given in a restricted range of doses as a 1-hour infusion because of its linear pharmacokinetics. Docetaxel is administered every 3 weeks. There is a significant response rate –relationship : the response rate in patients receiving 60mg/m², 75 mg/m² and 100 mg/m² in a recent study (réf. ??) was respectively 22.1, 23.3, 36 % and the time to progression 13.7, 13.9, 18.6 weeks. But an increase in hematologic and non-hematologic toxicity was noted with increasing dose.

The administration schedule of paclitaxel could be every 3 weeks as a 3-hour infusion or a weekly administration schedule with a relative lack of severe hematologic and non hematologic toxicity. Weekly administration of paclitaxel improves the response rate and decrease the hematologic toxicity compared with 3 weeks schedule, but increased neurotoxicity and therapeutic costs.

Vinorelbine, an antitubulin agent, it does have a favorable toxicity profile and significant antitumor activity, with response rate ranging from 34% to 41%. It could be a number of new administration schedules besides the classic administration is weekly IV perfusion but it is available in an oral formulation.

Combination Chemotherapy

The principle of non-overlapping mechanisms of resistance and toxicities has been the basis for applying combination chemotherapy. Although combination chemotherapy has been widely enhanced, the validity of this concept has not been confirmed in breast cancer. In several randomized trials comparing combination chemotherapy to single agent therapy, response rates are higher in the combination arm, and times to first progression are longer. However, overall survival has only been minimally improved at best. An overview including 106 randomized trials that focused on five major chemotherapy strategies is summarized in table 10.2.

The main findings from this overview concerning chemotherapy are summarized as follow: response rate is increased by polychemotherapy, compared with monochemotherapy; polychemotherapy with anthracyclines, compared with polychemotherapy without anthracyclines; polychemotherapy other than combination therapy with cyclophosphamide, methotrexate, and fluorouracil (CMF) compared with CMF regimens; more intensive chemotherapy regimens compared with less intensive chemotherapy regimens; and chemoendocrine therapy compared with chemotherapy alone.

In general, higher response rates were accompanied by definite increases in the occurrence of World Health Organization grade 3-4 toxicities. With only two comparisons was a clinically modest but statistically significant survival benefit found: (1) polychemotherapy versus single-agent chemotherapy and (2) cytotoxic agents delivered at higher doses or for longer periods versus less intensive cytotoxic regimens. Thus, polychemotherapy reduced the risk of death by 18% and, more intensive chemotherapy by 10%, translating in each case into a 5% to 6% absolute survival benefit at 2 years. In spite of the fact that combined cytotoxic therapies are more efficient if response rate is the major criteria, monotherapy cytotoxic therapy can be discussed if overall survival is the main criteria.

The important points gleaned from the overview are that (1) short inadequate-dose chemotherapy regimens should be avoided; (2) CMF or anthracycline-based or taxane (alone or in combination) regimens are reasonable treatment options for many metastatic patients, and ways of identifying those patients most likely to benefit from anthracyclines are needed; (3) chemotherapy and endocrine therapy should not be routinely combined; and (4) careful attention must be paid to treatment side effects and their impact on quality of life, given the narrow therapeutic index of cytotoxic agents and their modest impact on survival.

An important question is to know whether to use a combined therapy versus single chemotherapy agent. Randomized comparisons of combination therapy with the same agents used in a sequential therapy do not show any difference in overall survival. But combined therapy improves the response rate and the time to progression and is often preferred for patients with excellent performance status and who have a symptomatic metastatic disease.

It seems now that there is no place for the stem-cell supported high-dose chemotherapy, the highly toxic and costly strategy, with its as yet undefined impact on survival, remains difficult to justify outside the context of a prospective randomized clinical trial.

Strategy Under Study	No. of Patients		Response	
	No. of Trials	Total	Odds Ratio	95% CI
PCT versus single-agent therapy	15	2442	1.79	1.51-2.12
PCT with A versus PCT without A	30	5241	1.30	1.16-1.46
Other PCT versus CMF therapy	17	3041	1.22	1.05-1.42
More intensive CT versus less intensive CT	19	3193	1.67	1.43-1.95
CT+ HT versus CT alone	25	3606	1.56	1.36-1.80
Total	106	17523		

Abbreviations: A, anthracycline; CI, confidence interval; CMF, cyclophosphamide, methotrexate, and Fluorouracil chemotherapy; HT, hormonal therapy; PCT, polychemotherapy.

Table 10.3. Overview of Metastatic Breast Cancer Treatment, 1975-1997: Chemotherapy

Guidelines for selection of the sequence of chemotherapeutic agents is shown in (Fig. 10.2.)

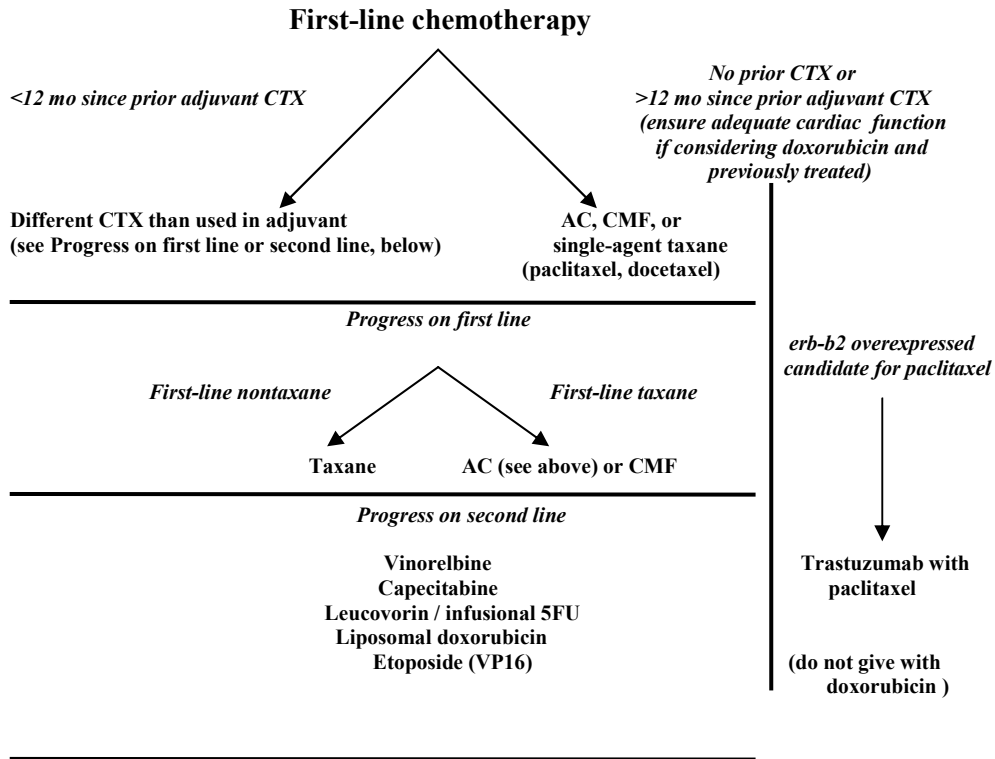


Figure 10.2. Decision Algorithm for Patients with Metastatic Breast Cancer

Targeted therapy

HER-2/neu, a new member of the group 1 growth factor receptor family, is amplified and /or overexpressed in 20% to 30% of patients with breast cancer. Overexpression of this oncogene product is associated with increased rates of tumor growth, enhanced rates of metastasis, shorter disease-free survival, and overall survival.

As a single agent, trastuzumab produces complete and partial remission in 13% to 20% of patients with metastatic breast cancer. In association with chemotherapy, trastuzumab enhances the response rate of the combination compared with chemotherapy alone and result in prolonged time to progression and increases 1-year survival rates. Trastuzumab is well tolerated, low-grade fever, chills, fatigue, and constitutional symptoms occur primarily with the first infusion, and serious

adverse effects are infrequent. In association with anthracycline chemotherapy, an increased incidence of subclinical and clinical cardiac toxicity has been observed.

There is compelling evidence to consider the use of trastuzumab in the initial management of women with HER-2/neu positive, hormone refractory metastatic breast cancer, however, there are a multitude of unanswered questions about the use of trastuzumab Herceptin in clinical practice. Cardiac toxicity It is unknown how long trastuzumab Herceptin should be administered and whether it should be continued with second-line chemotherapy after disease progression.

Recently two others targeted therapies are proposed alone or in association with chemotherapy. A murine anti VEGF antibody bevacizumab given as monotherapy demonstrated a modest activity in pretreated patients. It can be associated with chemotherapy (capecitabine or taxanes) and with hormonal treatment.

Lapatinib a tyrosine kinase inhibitor for patients with positive expression of HER 2 is proposed if failure of trastuzumab The main Side effects : fatigue nausea, cutaneous eruptions, diarrheas, skin dryness Acné.

Toxicity of those treatments are not to be neglected en citer quelques unes ...
Actually, their cost very high (for a benefit which is not obvious regarding the overall survival) is an important limiting factor of their use.

Bisphosphonates in the treatment of Bone Metastasis

Bone is the most common site of metastasis in breast cancer. Bone metastases are also the most common cause of morbidity, including serious and sometimes catastrophic complications such as pathologic fractures, hypercalcemia of malignancy, and spinal cord compression. Approximately 20% of patients who develop bone metastases have only bone metastases for protracted periods.

Bisphosphonates are a large family of hypophosphate analogs that inhibit osteoclast activity by interfering with osteoclast binding to the osteoid surface, recruitment of osteoclast precursors, and secretion of osteoclast-activating factors by tumor cells.

Treatment with bisphosphonate in women with lytic lesions has become a standard of practice. It has an important effect on the frequency of bone-related complications such as pain, the need for palliative radiation and hypercalcemia. But bisphosphonates have some side effects : risk of renal insufficiency and jaw osteonecrosis need a renal follow-up and stomatis check-up before starting the treatment

LOCAL TREATMENT

We can ask to Omar Omar to write several lines about hepatic surgery. Have you colleagues to write something about orthopedie and for thoracic and neurological treatment.