clinical recommendations

doi:10.1093/annonc/mdp115

# Locally recurrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up

F. Cardoso[1] & M. Castiglione[2]

On behalf of the ESMO Guidelines Working Group*

[1]Department of Medical Oncology, Jules Bordet Institute, Brussels, Belgium; [2]Institute of Social and Preventive Medicine (ISPM), University of Geneva, Geneva, Switzerland

## incidence

Breast cancer is the most common cancer in women in many countries, including developing countries. The crude incidence in the European Union is 109.8/100 000, the mortality is 38.4/100 000 women/year. Since 1990 the incidence rate has increased 1.5% annually. Due to advances both in early detection and in adjuvant treatment, mortality rates from breast cancer have been decreasing steadily in most western countries since the early 1990s. However, it is still the leading cause of cancer mortality in women. Approximately 6% of breast cancers are metastatic at diagnosis with a 5-year survival rate of 21%. Depending on prognostic factors, in the worst scenario, up to 30% of node-negative and up to 70% of node-positive breast cancers will relapse. The prevalence of metastatic disease is high because many women live with the disease for several years.

## diagnosis

- Clinical suspicion must be confirmed by radiologic and/or scintigraphic examinations and blood tests.
- Effort should be made to obtain histopathological confirmation particularly in the situation of an isolated metastatic lesion. Biological markers important for treatment decisions, such as hormonal receptors and HER-2 status, should be evaluated in the metastatic lesion whenever possible.

## staging and risk assessment

- Complete history, including menopausal status and co-morbidities; detailed history of the primary tumor, its biology, management and last normal follow-up (Table 1).
- Detailed physical examination including performance status.
- Blood tests: complete blood count, liver and renal function tests, alkaline phosphatase, calcium, tumor marker CA 15-3.
- Chest X-ray or computed tomography (CT), abdominal ultrasound or CT should be used to identify visceral disease.
- Bone scintigraphy, with confirmation of lesions by X-ray/CT/magnetic resonance imaging (MRI).
- CT and/or MRI of the central nervous system should be symptom driven.
- PET/PET–CT may be useful for identifying the site of relapse, particularly when traditional imaging methods are equivocal or conflicting. It may also be helpful to identify an isolated metastatic lesion, since this subset of patients may benefit from a more aggressive multidisciplinary approach.
- Estrogen and progesterone receptors, HER-2 receptors and proliferation markers of the metastatic lesion should be obtained, if possible, and particularly if not available on the primary tumor.

## treatment

- Isolated local–regional recurrence should be treated like a new primary with a curative intent including 'secondary' adjuvant treatment modalities as appropriate [II, B].
- The management of metastatic breast cancer (MBC) should involve all appropriate specialities in a multi/interdisciplinary team (medical, radiation, surgical and imaging oncologists, palliative care specialist, psychosocial support), and patients should be offered personalized appropriate psychosocial, supportive and symptom-related interventions as a routine part of their care.
- There are few proven standards of care in MBC management, therefore well-designed, independent, prospective randomized trials are a priority.
- The vast majority of MBC is incurable and hence the main treatment goal is palliation, with the aim of maintaining/improving quality of life, and possibly improving survival.
- The realistic treatment goals should be discussed with the patient and her family from the beginning and the patient should be encouraged to actively participate in all decisions. Patient's preferences should always be taken into account.
- Systemic treatment options for MBC are endocrine therapy, chemotherapy and biological agents such as trastuzumab and lapatinib [I, A].

*Correspondence to: ESMO Guidelines Working Group, ESMO Head Office, Via L. Taddei 4, CH-6962 Viganello-Lugano, Switzerland;
E-mail: clinicalrecommendations@esmo.org

Approved by the ESMO Guidelines Working Group: August 2003, last update December 2008. This publication supercedes the previously published version—Ann Oncol 2008; 19 (Suppl 2): ii11–ii13.

Conflict of interest: The authors have reported no conflicts of interest.

**Table 1.** Factors to consider in risk assessment and treatment decision making for MBC

| Disease-related factors | Patient-related factors |
|---|---|
| Disease-free interval | Patient's preferences |
| Previous therapies and response | Biological age |
| Biological factors (hormonal receptors, HER-2) | Menopausal status |
| Tumor burden (number and site of metastases) | Co-morbidities and performance status |
| Need for rapid disease/symptom control | Socio-economic and psychological factors |
| Available therapies in the patient's country | |

**Table 2.** Available endocrine therapies for MBC

| Class of agent | |
|---|---|
| Selective estrogen receptor modulators | Tamoxifen; toremifene |
| Estrogen receptor down-regulator | Fulvestrant |
| Luteinizing hormone-releasing hormone analogues | Goserelin; leuprorelin |
| Third-generation aromatase inhibitors | |
| Non-steroidal | Anastrozole, letrozole |
| Steroidal | Exemestane |
| Progestins | Medroxyprogesterone acetate; megestrol acetate |
| Androgens | |
| Anabolic steroids, e.g. nandrolone decanoat | |

- Radiation therapy is an integral part of palliative treatment.
- For limited metastatic presentations surgery may be considered.
- Bisphosphonates should be used for the treatment of hypercalcemia, to palliate symptoms and decrease risk of bone events from clinically evident bone metastases [I, A]. The timing and optimal duration of bisphosphonates are unknown.

## patients with luminal-type breast cancer (hormone receptor-positive breast cancer)

- Endocrine therapy is the preferred option except if clinically aggressive disease mandates a quicker response or if there are doubts regarding the endocrine responsiveness of the tumor. Available endocrine agents are listed in Table 2.
- The choice of endocrine agent should be individualized according to the patient's safety profile, co-morbidities and tumor biology.
- Maintenance with hormonal treatment after chemotherapy has not been established, but is a reasonable approach.
- Concomitant chemo-hormonal therapy is discouraged.

*premenopausal patients.* If no prior adjuvant tamoxifen or if discontinued for >12 months: tamoxifen with ovarian ablation (luteinizing hormone releasing hormone analogue or surgery) is the preferred option [I, B]. Otherwise, third-generation aromatase inhibitors may be considered after or concomitantly with ovarian ablation.

*postmenopausal patients.* If no prior adjuvant third-generation aromatase inhibitors (anastrozole, letrozole, exemestane) these are the preferred option since they have consistently shown superior results to tamoxifen as first-line therapy in terms of response rate, time to progression and, for letrozole, in 2-year overall survival [II, A]. However, tamoxifen remains an acceptable first-line therapy in selected cases.

Second-line hormone therapy may include tamoxifen, anastrozole, letrozole, exemestane, fulvestrant, megestrol acetate and androgens. No definitive recommendation can be given for endocrine treatment cascade, and particularly, the best option after progression on a third-generation aromatase inhibitor is currently unknown.

Patients with clear evidence of endocrine resistance should be offered chemotherapy or participation into clinical trials.

## patients with basal-type breast cancer (hormone receptor-negative breast cancer)

- Patients having hormone receptor-negative tumors are candidates for cytotoxic chemotherapy. Available agents/regimens are listed in Table 3.
- The only standard of care with level 1 evidence is the use of a taxane-based regimen as first-line therapy in patients progressing after adjuvant anthracycline-based chemotherapy [I A]. The selection of the best agent/regimen should be individualized and should take into account the factors listed in Table 1.
- For the majority of patients, overall survival outcomes from the sequential use of single cytotoxic drugs is equivalent to that of combination chemotherapy, with less associated toxicity and better quality of life. Therefore, in the absence of the need for a rapid and significant response for symptom control or life-threatening disease, preference should be given to the sequential use of a single cytotoxic agent. However, very few randomized clinical trials have correctly addressed this question and there is an urgent need for a well-designed, prospective randomized trial to compare sequential single-agent with combination chemotherapy as first-line therapy of MBC.
- There is no standard approach for patients requiring second- or further-line treatment since there are no data supporting the superiority of any particular regimen.
- Duration of each regimen and number of regimens should be tailored to each individual patient. Continuing beyond third-line may be justified in patients with good performance status and response to previous chemotherapy.
- High-dose chemotherapy should not be proposed.

## patients with HER-2-positive breast cancer

- Patients should be treated with trastuzumab with or without chemotherapy [II, B].
- Trastuzumab should be offered early to all HER-2-positive MBC patients.

**Table 3.** Selection of available chemotherapy agents/regimens for MBC

| |
|---|
| Non-anthracycline-containing |
| Cyclophosphamide/methotrexate/fluorouracil (CMF) |
| Platinum-based combinations (e.g. cisplatinum + 5-fluorouracil) |
| Capecitabine |
| Vinorelbine |
| Gemcitabine |
| Capecitabine + vinorelbine |
| Vinorelbine ± gemcitabine |
| Oral cyclophosphamide with or without methotrexate (metronomic chemotherapy) |
| Anthracycline-containing |
| Epirubicin monotherapy (weekly or 3-weekly) |
| Doxorubicin/cyclophosphamide or epirubicin/cyclophosphamide |
| Liposomal doxorubicin with or without cyclophosphamide |
| Fluorouracil/doxorubicin/cyclophosphamide |
| Fluorouracil/epirubicin/cyclophosphamide |
| Taxane-containing |
| Paclitaxel monotherapy weekly |
| Docetaxel monotherapy 3-weekly or weekly |
| Doxorubicin/taxane (paclitaxel or docetaxel) |
| Epirubicin/taxane (paclitaxel or docetaxel) |
| Docetaxel/capecitabine |
| Paclitaxel/gemcitabine |
| Paclitaxel/vinorelbine |
| Paclitaxel/carboplatin |
| New cytotoxic agents |
| Ixabepilone |
| Abraxane (nab-paclitaxel) |

- Cardiac monitoring should be performed before and while on trastuzumab therapy.
- Trastuzumab in combination with endocrine therapy is currently under scientific evaluation and the EGF 30008 trial investigating letrozole ± lapatinib has just been closed to accrual.
- The bulk of retrospective data and results of the phase III randomized Trial Beyond Progression show that continuing trastuzumab after the first disease progression, associated with a different chemotherapy regimen is superior to the discontinuation of this agent. With the approval of lapatinib for the treatment of MBC, the question of continuing trastuzumab or changing to lapatinib at the time of first progression remains open
- Lapatinib has shown a significant increase in time to progression in combination with capecitabine in patients progressing after trastuzumab.
- Other anti-HER-2 or pan-anti-HER agents, such as pertuzumab and HKI-272, are currently under investigation as are combinations of trastuzumab with other biological agents with or without chemotherapy to tackle the problem of resistance to trastuzumab.

### other biological agents

- Several biological or targeted agents are currently under active investigation as single agents or in combination.
- Bevacizumab, an anti-angiogenic agent, has been approved by the FDA and the EMEA for use in combination with paclitaxel as first-line treatment of MBC. However, a second randomized phase III trial did not confirm the value of bevacizumab in an unselected breast cancer population, and efforts must be made to clearly identify who may benefit from this expensive therapy. Sunitinib, a potent inhibitor of several tyrosine kinases, having anti-angiogenic and anti-proliferative effects, is in phase III trials for both HER-2-negative and HER-2-positive breast cancer.

## response evaluation

- Response evaluation is recommended after 3 months of endocrine therapy and after two or three cycles of chemotherapy by clinical evaluation, subjective symptom evaluation, blood tests and repeating the initially abnormal radiologic examinations with comparative measures. However, the interval between assessments should be tailored to the clinical needs of the patient and to the aggressiveness of the disease
- Serum tumor markers (CA 15-3) may be helpful in monitoring response, particularly in the case of not easily measurable disease, but should not be used as the only determinant for treatment decision.
- The role of PET/PET–CT in response assessment is still under investigation.

## follow-up

- Follow-up after the treatment of local–regional recurrence may be carried out as for primary breast cancer.
- Patients with MBC must be seen frequently enough to provide best possible palliation of symptoms and quality of life, which means on average every 2–3 months if on endocrine therapy and every one or two cycles of chemotherapy.

## note

Levels of evidence [I–V] and grades of recommendation [A–D] as used by the American Society of Clinical Oncology are given in square brackets. Statements without grading were considered justified standard clinical practice by the experts and the ESMO faculty.

## literature

1. ESO-MBC Task Force. Metastatic breast cancer. Recommendations proposal from the European School of Oncology (ESO)-MBC Task Force. Breast 2007; 16: 9–10.
2. Kataja V, Castiglione M. Locally recurrent or metastatic breast cancer: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Ann Oncol 2008; 19 (Suppl 2): ii11–ii13.
3. Network NCC. 2008. NCCN Clinical Practice Guidelines in Oncology: Breast Cancer, Version 2. In Edition 2008.
4. Colozza M, de Azambuja E, Personeni N et al. Achievements in systemic therapies in the pre-genomic era in metastatic breast cancer. Oncologist 2007; 12: 253–270.

5. Chan S, Friedrichs K, Noel D et al. Prospective randomized trial of docetaxel versus doxorubicin in patients with metastatic breast cancer. J Clin Oncol 1999; 17: 2341–2354.
6. O'Shaughnessy J, Miles D, Vukelja S et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline-pretreated patients with advanced breast cancer: phase III trial results. J Clin Oncol 2002; 20: 2812–2823.
7. Albain KS, Nag SM, Calderillo-Ruiz G et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment: final results of a global phase III study. J Clin Oncol 2008; 26: 3950–3957.
8. Burstein HJ, Kuter I, Campos SM et al. Clinical activity of trastuzumab and vinorelbine in women with HER2-overexpressing metastatic breast cancer. J Clin Oncol 2001; 19: 2722–2730.
9. Miller K, Wang M, Gralow J et al. Paclitaxel pus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 2007; 357: 2666–2676.
10. Gennari A, Amadori D, De Lena M et al. Lack of benefit of maintenance paclitaxel in first-line chemotherapy in metastatic breast cancer. J Clin Oncol 2006; 24: 3912–3918.
11. Ghersi D, Wilcken N, Simes J et al. Taxane containing regimens for metastatic breast cancer. Cochrane Database Syst Rev 2003; 3: CD003366.