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AGO Recommendations for Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2013

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Guidelines · Locoregional relapse · Metastatic breast cancer · Targeted therapy

Introduction

For the last 12 years, the Breast Committee of the Arbeitsgemeinschaft Gynäkologische Onkologie (German Gynaecological Oncology Group, AGO) has issued annually updated evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer. The AGO Breast Committee consists of 43 gynaecological oncologists specialized in breast cancer and interdisciplinary members specialized in pathology, radiological diagnostics, medical oncology and radiotherapy. Each update is performed according to documented rules by thoroughly reviewing and scoring chapter by chapter the recent publications for their scientific validity (Oxford Level of Evidence, LoE; *www.cebm.net* [1]) and clinical relevance (AGO Grades of Recommendation; table 1). All AGO Breast Committee members have declared their potential conflicts of interest. Here, we present the 2013 update of these guidelines focussing on changes made this year. The full version of the 2013 update is available online as a PDF file [2] in an English and a German version. Moreover, a version for patients is also available at *www.ago-online.de.*

Locoregional Recurrence

On average, 5–10% of primary breast cancer patients will develop locoregional recurrence after primary adjuvant treatment. The molecular subtype is an important risk factor. Patients with triple-negative or human epidermal growth factor receptor 2 (HER2)-positive subtype are more likely to

Table 1. AGO grades of recommendation

++	This investigation or therapeutic intervention is highly beneficial for patients, can be recommended without restriction, and should be performed.
+	This investigation or therapeutic intervention is of limited benefit for patients and can be performed.
+/–	This investigation or therapeutic intervention has not shown benefit for patients and may be performed only in individual cases. According to current knowledge a general recommendation cannot be given.
–	This investigation or therapeutic intervention can be of disadvantage for patients and might not be performed.
–/–	This investigation or therapeutic intervention is of clear disadvantage for patients and should be avoided or omitted in any case.

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develop local recurrence compared to those with luminal A/B subtype [3]. To avoid 'overtreatment' or 'undertreatment' and to prevent complications, restaging is recommended. In addition, the recurrence should be confirmed by a biopsy, and the predictive markers including oestrogen receptor (ER), progesterone receptor (PR) and HER2 should be re-evaluated. The aim of surgery is to achieve an 'in sano resection'. The management of the axilla is challenging. In a cN0 situation, performing sentinel lymph node biopsy (SLNB) during relapse surgery (second SLNB) after previous SLNB is technically feasible [4, 5]. However, if no sentinel can be identified, axillary lymph node dissection should not be performed. Only if axillary lymph nodes are suspicious, exploratory axillary dissection is indicated. Irradiation of the axilla in the case of axillary recurrence depends on previous treatment and should be individually discussed. Cytotoxic treatment should be offered particularly to those patients who are hormone receptor (HR)-negative based on the results of the CALOR trial [6]. 'Adjuvant' chemotherapy resulted in a significant benefit for disease-free survival (DFS) and overall survival (OS) following isolated locoregional recurrence compared to no chemotherapy. HER2-targeted therapy and endocrine therapy are recommended in HER2-positive and in HR-positive patients, respectively. In non-curative cases and where there is a lack of other therapeutic options, combination of radiotherapy and hyperthermia improves the clinical response rate but should only be performed in expert centres (as listed on the website of the Deutsche Krebsgesellschaft, DKG) [7]. Other options are chemotherapy combined with hyperthermia, electrochemotherapy and photodynamic therapy, which may provide clinical benefit in individual patients [8, 9].

Endocrine and Targeted Therapy in Metastatic Breast Cancer

Endocrine therapy in metastatic breast cancer remains the therapy of choice in HR-positive disease. If feasible, a biopsy from the metastatic lesion should be taken. Recent prospective and retrospective data indicate a receptor shift in about 15% for ER, between 25–40% for PR, and in less than 10% for the HER2 status [10–13].

HER2-Negative Metastatic Breast Cancer

In premenopausal patients the possible therapeutic option of a luteinizing hormone-releasing hormone (LHRH) analogue in combination with fulvestrant has been included. Although only 26 patients in different lines have been treated with that combination as reported recently, the treatment option has been included [14].

In postmenopausal patients there are several endocrine treatment options. The updated analysis of the CONFIRM study supports the use of 500 mg fulvestrant. After adjuvant aromatase inhibitor (AI), it has become one of the preferred options in the 1st or 2nd line endocrine treatment for primary breast cancer. 250 mg fulvestrant remains an option which has been proven equally effective as an AI [15]. 2 trials reported their final analysis on the combination of fulvestrant 250 mg plus anastrozole vs. anastrozole alone. The US trial performed by the SWOG group indicated a significant prolonged progression-free survival (PFS) and OS for the combination [16], whereas the FACT study could not confirm these findings [17]. Due to these conflicting results the combination after adjuvant tamoxifen was considered an option (+/–).

The combination of everolimus and exemestane is been recommended for 2nd line therapy in women who have received tamoxifen as adjuvant therapy. For women who have already been treated with a non-steroidal AI in the adjuvant setting and have relapsed within 12 months, everolimus plus exemestane is one recommended treatment option. Termsirolimus plus letrozole however is not a treatment option [18] (figs. 1 and 2). The combination of everolimus plus tamoxifen has been upgraded as a treatment recommendation based on the data of the TAMRAD study [19, 20].

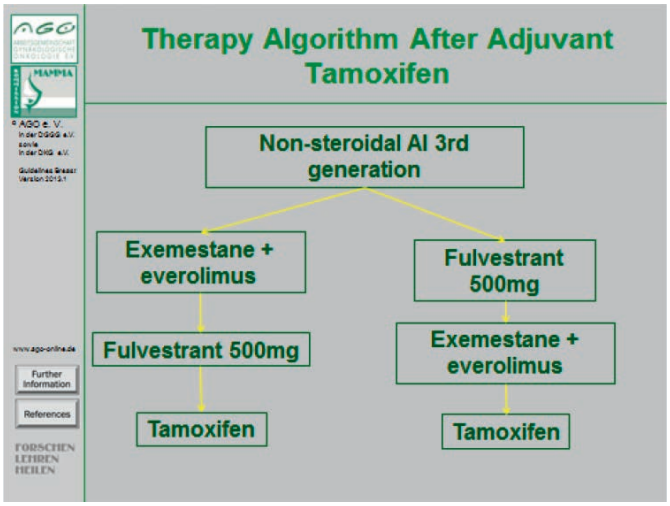

Fig. 1. Therapy algorithm after adjuvant tamoxifen.

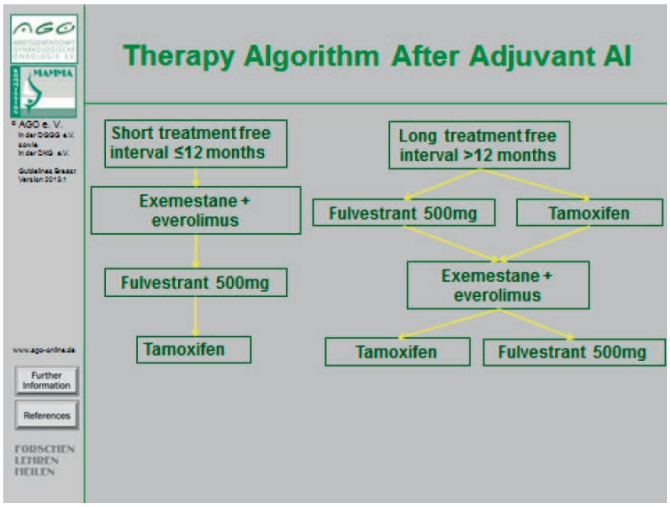

Fig. 2. Therapy algorithm after adjuvant aromatase inhibitor (AI).

The combination of an endocrine therapy plus bevacizumab has not been proven to be superior to endocrine therapy (mostly letrozole) alone [21, 22].

HER2+ Metastatic Breast Cancer

HER2+ HR-positive breast cancer can generally be treated with an endocrine therapy in combination with an anti-HER2 agent. There are no new data supporting that concept. However, with the dual anti-HER2 blockade at the horizon this might change. So far, there are no data for metastatic breast cancer to support this concept.

Chemotherapy with or without Targeted Drugs in Metastatic Breast Cancer

For the 2013 update, we have combined the chapters 'chemotherapy' and 'targeted therapy' for metastatic breast cancer, acknowledging the increasing role of targeted therapies which are generally given in combination with standard endocrine or cytotoxic therapies and provide survival benefit in some circumstances (LoE 1b). Similar to the treatment selection in the adjuvant situation, also in advanced disease, tumour biology is considered relevant for therapy decisions. The choice of treatment depends on i) ER/PR, HER2; combination with compounds of targeted treatment; ii) previous treatments (and their toxicities); iii) aggressiveness of disease and location of metastases; iv) biologic age; v) co-morbidities (including organ dysfunction); and vi) patient preference and expectations.

First-line therapy in ER-positive tumours is generally endocrine therapy. If the disease has been proven to be ER-negative (preferentially diagnosed by biopsy of at least 1 metastatic lesion), or if the course of the disease suggests endocrine resistance or urgent need of response, cytotoxic chemotherapy is indicated (LoE 1aA, AGO++). This is in accordance with recently published First International Consensus Guidelines for Advanced Breast Cancer (ABC 1) [23]. The use of anthracyclines (including liposomal anthracyclines) and taxanes remains state of the art in 1st-line therapy of metastatic breast cancer. Vinorelbine, capecitabine and nab-paclitaxel are reasonable alternatives. Monotherapy is preferred over polychemotherapy in non-life-threatening situations. Particularly in single-agent therapy, it is recommended to treat as long as the therapeutic index remains positive (LoE 2bB, AGO+). Monitoring of treatment response should be performed by assessing tumour burden at baseline and approximately every 2 months, i.e. every 2–4 cycles of treatment. Assessment of a target lesion may be sufficient. In slow growing disease, longer intervals are acceptable (AGO++). Although some evidence is already available, determination of circulating tumour cells is still considered experimental and recommended preferentially within clinical trials (LoE 1bA, AGO+).

In some situations, e.g. in triple-negative breast cancer or other aggressive situations, combination of chemotherapy with bevacizumab can be recommended to increase the response rate and PFS although not prolonging survival (LoE 2bB, AGO+) [24]. The combination of chemotherapy with other targeted drugs (e.g. sunitinib, sorafinib, vantetanib) is experimental and should not be performed outside of clinical trials. Platinum-based chemotherapy may be useful as further-line treatment especially in triple-negative breast cancer (LoE 2bB, AGO+/–), even though data from prospective randomized trials are still lacking.

The biggest step forward in the treatment of metastatic breast cancer has been achieved in HER2-overexpressing disease. Recently, pertuzumab was registered in the European market for 1st-line patients as a triplet together with trastuzumab and docetaxel. Approval was based on emerging data of the phase III CLEOPATRA trial that demonstrated an improvement of PFS (primary endpoint) and OS compared to docetaxel and trastuzumab alone [25].

In the light of this upcoming 1st-line standard, the sequential use of anti-HER2 drugs needs to be redefined in the near future. In this context, introduction of trastuzumab emtansine (T-DM1) as a further option is eagerly awaited. T-DM1 is the first member of a new class of antibody-drug conjugates (ADC) with proven activity in solid tumours. It is composed of trastuzumab, a stable linker molecule, and the cytotoxic DM1 (derivate of maytansine). As a consequence, T-DM1 combines the distinct mechanisms of action of both DM1 and trastuzumab. Clinical relevance of these findings has been demonstrated in the pivotal EMILIA trial that focused preferentially on heavily pretreated BC patients. One of the main inclusion criteria was pre-exposure to taxanes and trastuzumab. The recently published results indicate that T-DM1 is superior to lapatinib and capecitabine in terms of PFS and OS. Furthermore, toxicity was analysed as another endpoint, suggesting that the experimental compound was better tolerated [26, 27]. With respect to its favourable safety profile, T-DM1 represents the next step in modern targeted drug design in order to minimize chemotherapy-induced side effects in HER2-positive patients.

Specific Sites of Metastases

Specific sites of breast cancer metastases are liver, lung, pleura, pericardium, peritoneum, bone marrow, or any soft tissue. Other rare locations like adrenals, ovaries, uterus, stomach, colon, or placenta have also been reported. In such rare cases, controlled trials are not eligible, and treatment options must be discussed individually.

Management of primary stage IV breast cancer focuses on systemic therapy. The impact of the extent of local treatment on OS is still under discussion. Some trials have suggested an association between local treatment (surgery or radiotherapy)

of the primary tumour and prolonged survival, whereas there are other reports that did not [28]. However, many questions remain, such as whether these results reflect a selection of women with good prognosis for primary site therapy; other questions address the fraction of women in published studies who were diagnosed with metastatic disease only after surgery, whether specific subsets of metastases and biological subtypes would derive greater benefit, and the appropriate timing and extent of local therapy. If surgery of the primary tumour is performed in the metastatic setting, local excision or mastectomy should be done with tumour-free margins [29–33]. Axillary surgery is only indicated for bulky disease.

Systemic treatment of metastatic disease is the therapy of choice. Before treatment, metastases should be confirmed by histology to re-evaluate diagnosis, HR and HER2 status. A shift in these markers occurs in nearly 20% and has an impact on systemic treatment. If surgery for distant metastases is considered, good overall health, oligometastasis and a long time between primary treatment and the occurrence of metastases are all favourable factors regarding outcome. Resection of liver metastases may be performed after histological verification if R0 resection is feasible, if no extrahepatic metastases were present, and in patients who had HR-positive breast cancer and a good response to former chemotherapy [34, 35]. Other procedures like regional radiotherapy, thermoablation or chemoembolization are also possible in individual cases [36, 37].

For proven pulmonary metastases, the LoE for a curative approach is low, but some patients might benefit from a metastasectomy followed by an appropriate systemic treatment [38]. In accordance with the treatment of liver metastases, resection of lung metastases should only be performed if R0 resection is feasible and if histological verification was done. The timing of any local intervention may be critical; resection before progression is associated with a better outcome.

About 10% of all breast cancer patients develop malignant pleural effusion (MPE). In almost 50% of MPE it is the first sign of metastatic disease, resulting in dyspnoea and reduced subjective well-being. It should be treated in symptomatic cases exclusively. Thoracoscopy with talcum pleurodesis (VATS) is the option of choice for MPE. Other sclerosing but more rarely used agents are bleomycine, doxycycline and mitoxantrone [39]. Continuous pleural drainage with indwelling pleural catheters is a well-tolerated and safe treatment alternative for patients who are not candidates for VATS. Catumaxomab is not yet recommended for MPE.

Overall, 3% of breast cancer patients will suffer from malignant ascites. Management of ascites takes place in the context of palliative care, and aims at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab [40] remains an option in individual cases.

Malignant pericardial effusion and cardiac tamponade remains a rarity in breast cancer patients. In symptomatic patients, drainage and pericardial fenestration are probably the treatment options of choice. For individual patients, VATS or ultrasound-guided puncture with instillation of mitoxantrone or bleomycine may be an alternative [41].

The choice between supportive care or specific anticancer treatment for poor performance status breast cancer patients with multimetastatic disease and pancytopenia due to bone marrow involvement often remains a clinical and human dilemma. Depending on the underlying cancer biology, endocrine or chemotherapy or antibody treatment options should be reconsidered [42]. It has been reported that aggressive combination treatment regimens were effective since most patients show improved marrow function after chemotherapy, and prolonged survival could be possible.

Soft Tissue Metastasis – Local Radiotherapy

Local radiotherapy is the most important treatment for patients with paresis or spinal cord compression, who cannot be operated on or have failed to respond to systemic treatment [43]. Even after surgery, concomitant radiotherapy and systemic treatment are indicated. Plexus infiltration and other inoperable soft tissue metastasis should be treated with radiotherapy.

Central Nervous System Metastases in Breast Cancer

Metastatic spread to the central nervous system is an increasing problem in triple-negative breast cancer as well as in HER2-positive disease. Nevertheless, screening for asymptomatic brain metastases (BM) on a routine basis is not recommended in breast cancer. A key problem is that most studies examining the treatment of BM did not focus on breast cancer. For many years, it has been debated whether patients with a limited number of BM may benefit from whole brain radiation therapy (WBRT) after local treatment of these lesions. A recent meta-analysis suggests that the standard of care in BM is 3,000 cGy in 10 daily fractions or 2,000 cGy in 4–5 daily fractions (LOE 1a, AGO++) [44]. Consistent with the 2012 recommendations, surgical procedures should be limited to individuals presenting with clinical symptoms or complications due to the location of the metastases. Evidence is suggesting that this is an individualized procedure as survival is not improved. The same Cochrane meta-analysis provides no evidence that combination of WBRT with either radiosensitizers or chemotherapy is of any benefit over WBRT alone [44]. In asymptomatic individuals with BM overexpressing HER2, the use of lapatinib and capecitabine may be an option to reduce signs and symptoms as well as to postpone the onset of WBRT as demonstrated in a phase II trial (LOE 2b, B; AGO+) [45].

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