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AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2017

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Introduction

For the last 16 years, the Breast Committee of the *Arbeitsgemeinschaft Gynäkologische Onkologie* (German Gynecological Oncology Group, AGO) has been preparing and updating evidence-based recommendations for the diagnosis and treatment of patients with early and metastatic breast cancer (MBC). The AGO Breast Committee consists of gynecological oncologists specialized in breast cancer and interdisciplinary members specialized in pathology, radiologic diagnostics, medical oncology, and radiation oncology. This update has been performed according to a documented rule-fixed algorithm, by thoroughly reviewing and scoring chapter by chapter recent publications for their scientific validity (Oxford level of evidence (LoE), *www.cebm.net*) [1] and clinical relevance (AGO grades of recommendation; table 1). We herewith present the 2017 update; the full version of the updated slide set is available online as a PDF file in both English and German [2]. Moreover, a special version for patients is also available at *www.ago-online.de*.

Bone Health and Osteooncology

Bone Metastasis

Osteoclast-inhibiting therapy including denosumab and bisphosphonates (BP) for reducing the risk of skeletal complications is the standard treatment for breast cancer patients with bone metastases. The approved schedule for zoledronic acid (4 mg i.v.) and denosumab (120 mg s.c.) is every 3–4 weeks. Due to concerns regarding the toxicity of these agents, including osteonecrosis of the jaw (ONJ), there has been increasing interest in the de-escalation of osteoclast inhibitors. In a recent study among patients with bone metastases from breast cancer, prostate cancer, or multiple myeloma, the use of zoledronic acid every 12 weeks (q12w) compared with the standard dosing interval of every 4 weeks (q4w) was associated with equal efficacy (prevention of skeletal events over 2 years); in addition, a numerical reduction in ONJ as well as a lower incidence of kidney dysfunction was noted [1]. Therefore, administration of zoledronic acid q12w (LoE 1a/A/AGO++) should be preferred over zoledronic acid q4w (LoE 1a/A/AGO+).

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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.

Over the past years, several randomized phase III trials have compared q4w to q12w zoledronate treatment after completion of several months of treatment with the q4w schedule (ZOOM trial, OPTIMIZE-2 trial) or upon treatment initiation (CALGB (ALLIANCE) 70604) [2–4]. No significant differences in the rate of skeletal-related events (e.g. pain, radiotherapy, fractures) were reported from these 3 trials.

The safety of less frequent dosing of osteoclast inhibitors is further supported by a meta-analysis by Ibrahim et al. [5] including 5 clinical trials. The summary risk ratio for on-study skeletal-related events in patients receiving standard (61/443 patients) versus less frequent dosing (49/392 patients) was 0.90 (95% confidence interval (CI) 0.63–1.29). Therefore, the switch from a 4- to a 12-weekly schedule after 1 year of monthly zoledronate may be an important option for MBC patients in order to reduce toxicities (LoE 1a/A/AGO+).

Clinical data addressing less than q4w dosing for denosumab are derived from only small phase II trials [6, 7]. Hence, a de-escalation approach for denosumab is currently not recommended (LoE 4/C/AGO-).

Follow-Up of Breast Cancer

One of the major goals of breast cancer follow-up is the early detection of curable breast cancer events, i.e. breast or locoregional recurrence (LoE 1a/B/AGO++) (suppl. fig. 1, *www.karger.com/?DOI=477576)*. Early detection of symptomatic metastases is desirable (LoE 3b/C/AGO+); however, with regard to the early detection of asymptomatic metastases (LoE 1a/A/AGO-), data are inconsistent and most importantly do not suggest a survival benefit. Beyond improvement of survival, additional issues like improvement of quality of life, physical performance, and the reduction of treatment-related side effects are important (LoE 2b/B/AGO+). In addition, re-evaluation of current adjuvant therapies and the assessment or improvement of treatment compliance (especially endocrine therapy) should be part of follow-up (LoE 5/D/AGO++). It should thus be pointed out that every patient has the right to obtain a second opinion (LoE 2c/B/AGO++); genetic counseling should be offered if indicated, as should hormone replacement, prophylactic surgery, and breast reconstruction (LoE 2c/C/AGO+). Further issues, such as pregnancy, contraception, sexuality, quality of life, menopausal symptoms, and specific psychological aspects, should be addressed proactively (LoE 4/C/AGO+).

Lifestyle modifications (cessation of smoking, diet, reduced alcohol consumption, physical activity) and interventions with regard to co-morbidities (diabetes) are further important aspects of follow-up. From a patient's perspective, examination of the breast, reassurance, guidance and answering questions, evaluation of treatment including side effects, and psychosocial support are also important.

Most importantly, follow-up examinations in asymptomatic patients in routine situations should not consist of tumor marker measurements, liver ultrasound, bone scans, X-ray, computed tomography (CT) or positron emission tomography scans, and monitoring of circulating tumor cells (CTCs). For the detection of curable events, imaging procedures such as mammography, ultrasound, and, in specific situations, magnetic resonance imaging in combination with self-examination and physical examination are recommended. In this context, screening for second malignancies according to guidelines (e.g. colorectal, endometrial, ovarian, or cervical cancer, lymphoma) is meaningful.

Further, a Dexa (dual-energy X-ray absorptiometry) scan at baseline and a repeat scan according to individual risk in women with premature ovarian failure or in women on aromatase inhibitor (AI) therapy is recommended [8].

Locoregional Recurrence

In patients with locoregional relapse, pretherapeutic biopsy to re-assess histology as well as estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status is strongly recommended (LoE 3b/B/AGO++) [9]. Besides well known clinical and pathological factors and molecular subtypes, obesity is associated with a higher risk of locoregional relapse, a shorter distant recurrence-free survival, and a shorter overall survival, regardless of menopausal status and time of onset of obesity. This was shown in a recent meta-analysis of 82 studies (n = 213,075) (LoE 1b) [10]. In addition, patients with triple-negative breast cancer (TNBC) and those with HER2-positive breast cancer without adjuvant trastuzumab treatment are at increased risk for locoregional relapse [11, 12]. Clinical consequences, however, of these initial reports remain to be determined.

With regard to surgical options, sentinel lymph node (SLN) dissection after prior SLN biopsy is not indicated, because all the necessary information for consequent therapeutic options will be derived from the tumor biology. Since there is no survival advantage, removing lymph nodes in the recurrent setting is not recommended (LoE 1b/B/AGO-) [13].

Axillary dissection should not be performed in cases with cN0 disease.

With regard to systemic therapy, the CALOR trial (n = 163; median follow-up 4.9 years) demonstrated a significant benefit for postoperative chemotherapy in patients with fully excised locoregional relapse, particularly in cases with ER-negative disease (LoE 2b/B/AGO+). The 5-year disease-free survival rates were 69% (95% CI 56–79) and 57% (95% CI 44–67) with and without chemotherapy, respectively (hazard ratio (HR) 0.59; 95% CI 0.35–0.99; p = 0.046) [14]. If chemotherapy is planned, a preoperative approach may be considered. In cases with HER2-positive disease, chemotherapy in combination with HER2-targeted therapy is a reasonable option (LoE 5/D/AGO+). It needs to be emphasized that patients with inoperable locoregional relapse were included in the pertuzumab registration trial CLEOPATRA [15].

In patients with ER-positive locoregional relapse following complete resection (R0), endocrine-based therapy is considered standard. In the case of (re-)recurrent disease in the ipsilateral breast or thoracic wall, the possibility of repeated radiotherapy (+/- hyperthermia) may be discussed (LoE 3a/C/AGO+/-). However, these patients seem to have an unfavorable prognosis [16].

Endocrine and Targeted Therapy in MBC

Endocrine therapy is the backbone of and first choice for the treatment of hormone receptor (HR)-positive MBC. In order to reliably determine the receptor status upon the diagnosis of MBC, it is encouraged to biopsy and re-access the HR status of the metastatic site whenever possible. Pooled relative discordance rates between primary tumors and metastatic disease for ER, PR, and HER2 status have been reported in 20% (95% CI 16–35%), 33% (95% CI 29–38%), and 8% (95% CI 6–10%) of cases, respectively [17]. However, even if analyses reveal endocrine sensitivity, tumor cells may have generated endocrine resistance. Within all lines of treatment, treatment options should take previous endocrine therapies, age and comorbidities, and drug approval status into consideration.

In peri- and premenopausal patients, ovarian function suppression (gonadotropin-releasing hormone (GnRH) analogue or luteinizing hormone analogue) is the first step of endocrine treatment. Whenever possible, it should be combined with tamoxifen 20 mg/day (LoE 1a/A/AGO++) [18]. GnRH analogues can also be combined with an AI or with fulvestrant if there are contraindications for tamoxifen. The addition of the new CDK4/6 inhibitor palbociclib to the combination of GnRH analogue plus fulvestrant significantly improved progression-free survival (PFS) (PALOMA-3 study) even in pretreated patients [19]. On this account, the combination of palbociclib + fulvestrant + GnRH analogue is highly recommended (LoE 2b/B/AGO++). For the combination of palbociclib + AI + GnRH analogue, data is limited (LoE 5/D/AGO+). However, monotherapy with ovarian function suppression or tamoxifen alone remains an option, but is not commonly considered standard of care.

In postmenopausal patients, endocrine treatment with fulvestrant 500 mg (LoE 1b/A/AGO++), an AI (crossed steroidal or non-steroidal AI depending on previous AI exposure), or tamoxifen (LoE 2b/B/AGO+) are recommended [20, 21]. The phase II PALOMA-1 trial showed a significant PFS advantage of 10 months regarding the combination of letrozole and palbociclib in the first-line setting [22]. The phase III PALOMA-2 trial confirmed the results impressively with an increase in PFS of again 10 months, which led to Federal Drug Administration (FDA) and European Medicines Agency (EMA) approval [23]. For this reason, palbociclib + letrozole is highly recommended (LoE 1b/B/AGO++). If the cancer progresses on therapy or shortly after, single-agent endocrine therapy, the combination of palbociclib with fulvestrant (LoE 1b/B/AGO++) [19], the combination of exemestane plus everolimus (LoE 1b/A/AGO+) [24], or the combination of possibly both letrozole + everolimus (LoE 2b[a]/B/AGO+/-) [25] or fulvestrant + everolimus (LoE 2b[a]/B/AGO+/-) [26] can be considered. In the case of disease progression on 1 of the named agents at a later stage, previous treatments could be repeated. Initiation of first-line bevacizumab parallel to endocrine therapy in the case of disease progression is not recommended as there are 2 studies with conflicting results (LoE 1b/B/AGO+/-) [27, 28] (suppl. fig. 2, *www.karger.com/?DOI=477576)*.

For patients with remission or at least stable disease after first-line chemotherapy in combination with bevacizumab, maintenance endocrine therapy can be considered individually (LoE 1b/B/AGO+/-) [29].

In HER2-positive/HR-positive advanced breast cancer, combinations of anastrozole or letrozole with trastuzumab, or letrozole with lapatinib, or fulvestrant with lapatinib, or very recently letrozole with trastuzumab + pertuzumab are therapeutic options [30–32]. However, PFS was quite short in these clinical trials. Combination therapies of induction chemotherapy plus HER2-directed treatment should be considered a more effective option.

Chemotherapy with or without Targeted Drugs in MBC

Treatment options in MBC are mainly based on the tumor biology of the primary tumor. If possible, re-biopsies of metastatic lesions are recommended to optimize treatment decisions using the information of the phenotype derived from the metastatic site. In retrospective series, there is evidence that survival could be improved by various treatment lines (LoE 2a), namely, by combining chemotherapy and targeted drugs whenever feasible (LoE 1b) [9].

Predictive Factors for Treatment Decisions

Treatment decisions in MBC are based on several predictive factors such as ER and PR status indicating that a response to palliative endocrine therapy is likely (LoE 1a/A/AGO++). A clinically meaningful remission during cytotoxic treatment speaks for the continuation of this treatment option (LoE 1b/A/AGO++). HER2 overexpression is a predictive marker for the use of anti-HER2-di-

rected drugs (LoE 1a/A/AGO++). In the case of bone metastases, bone-modifying drugs should be used (LoE 1b/A/AGO+) [9]. CTCs to monitor remission or progression of MBC might be a useful tool in the setting of a well-designed clinical trial (LoE 1b/A/AGO+). Outside of this setting, CTCs should be used with caution [33].

MBC Treatment – General Considerations

In MBC, it is important to be aware of patients' preferences and expectations and to discuss the rationale of the different treatment options. If chemotherapy is indicated, one has to reevaluate remaining toxicities from previous treatment lines, the treatment-free interval, e.g. from the end of adjuvant therapies, the location of the metastatic sites, and the total tumor burden. Pre-existing or treatment-related comorbidities are of special interest, along with the treatment expectations of the patient. It is helpful to have a realistic estimation of the lifetime remaining (AGO++) [34].

Primary and Secondary Endocrine Resistance

Endocrine therapy is the mainstay of targeted therapy in endocrine-sensitive MBC (LoE 1a/A/AGO++). In the case of progression, one has to differentiate between primary endocrine resistance defined as treatment failure while on adjuvant endocrine therapy within the first 2 years or within the first 6 months of first-line endocrine therapy for MBC and secondary endocrine resistance if progression occurs after the first 2 years of adjuvant endocrine therapy or in MBC if progression is detected after the first 6 months of treatment [9]. In endocrine-sensitive MBC, the introduction of endocrine therapy is recommended as long as no life-threatening situations are diagnosed (AGO++).

Chemotherapy in MBC

If chemotherapy is indicated in MBC, the use of monotherapy is recommended compared to a combination chemotherapy as long as the therapeutic index is positive (LoE 1a/A/AGO++) [9]. Assuming a positive therapeutic index, the preferred option is to treat until progression (LoE 2b/B/AGO+), compared with stopping treatment at best response (LoE 2b/B/AGO+/-). To change the chemotherapy regimen prior to progressive disease is not recommended (LoE 2b/B/AGO+/-). Treatment should be stopped in the case of progressive disease or intolerable toxicity (LoE 1c/A/AGO++) [35]. Compliance and adherence to any treatment in MBC, as well as performance status, toxicity, and clinical symptoms including the target lesion should be reevaluated on a regular basis every 2 months or every 2–4 cycles depending on the clinical context (LoE 1a/A/AGO++) [36].

Chemotherapy in MBC (HR-Positive, HER2-Negative) after Pretreatment with Anthracyclines

After pretreatment with anthracyclines, the first option is the use of taxanes, preferably weekly paclitaxel (LoE 1a/A/AGO++) or 3-weekly docetaxel (LoE 1a/A/AGO++) [37, 38]. Nab-paclitaxel as a weekly or 3-weekly schedule is an alternative option (LoE 2b/B/AGO++) [39]. Capecitabine, an orally available option causing no alopecia, is another valuable option (LoE 2b/A/AGO++). In addition, liposomal doxorubicin (LoE 2b/B/AGO+) and vinorelbine (LoE 2b/B/AGO+/-) are also available.

Chemotherapy in MBC (HR-Positive, HER2-Negative) after Pretreatment with Anthracyclines and Taxanes

Patients at risk are exposed to anthracyclines and taxanes either in the neoadjuvant or adjuvant setting. In the case of relapse, participation in clinical trials is recommended (AGO++). In clinical routine, capecitabine is the treatment of choice (LoE 2b/B/AGO++). Alternative monotherapy drugs are eribulin (LoE 1b/B/AGO++) and vinorelbine (LoE 2b/B/AGO++) [40]. When a re-challenge of previously given drugs is indicated, taxane rechallenge should not be performed within 12 months of the last taxane application (LoE 2b/B/AGO+) [41]. Liposomal doxorubicin might be used for the some indications (LoE 2b/B/AGO+). If symptoms indicate the use of combination chemotherapy, gemcitabine in combination with either platinum salts (LoE 2b/B/AGO+/-) or capecitabine (LoE 2b/B/AGO+/-) might be an option [42, 43]. In contrast, the combination of gemcitabine and vinorelbine is not recommended (LoE 1b/B/AGO-).

Management of Metastatic TNBC

Most patients are pretreated with anthracyclines and taxanes in early breast cancer. Thus, the introduction of carboplatin in first-line chemotherapy is superior to docetaxel (LoE 1b[a]/B/AGO+/-), specifically in patients with germline *BRCA* mutations (LoE 1b[a]/B/AGO+) [44]. Carboplatin might also be given in combination with gemcitabine (LoE 1b/A/AGO+) or in combination with nab-paclitaxel (LoE 2b[a]/B/AGO+) [45].

Recent data suggest that in TNBC the addition of bevacizumab to capecitabine (LoE 1b/B/AGO+) or paclitaxel weekly (LoE 1b/B/AGO+) is of substantial benefit if used in first-line MBC treatment [46–48].

Bevacizumab in the Management of HER2-Negative MBC

Bevacizumab is used as a targeted drug without evaluation of the target itself [46, 47]. It is widely used in the first-line setting in MBC in combination with paclitaxel weekly (LoE 1b/B/AGO+) or capecitabine (LoE 1b/B/AGO+). New data from the IMELDA trial suggest the use of capecitabine and bevacizumab as a maintenance therapy in patients with complete response, partial response, or stable disease after induction therapy with doxetacel and bevacizumab. This sequential approach improves survival over bevacizumab alone [49, 50]. Bevacizumab might also be used in combination with taxanes, capecitabine (LoE 1b/B/AGO+/-), or gemcitabine or vinorelbine (LoE 1b/B/AGO-) as second-line treatment. The evidence for using bevacizumab beyond the second line is limited (LoE 1b/B/AGO-). The recent release of data from the TANIA trial revealed that continuing bevacizumab beyond first and second progression of locally recurrent MBC improved second-line PFS, but no improvement in longer-term efficacy was observed [51].

First-Line Treatment in HER2-Overexpressing MBC

In HER2-overexpressing MBC, the standard of care is the dual horizontal blockade of the HER2/neu receptor by trastuzumab and pertuzumab in combination with docetaxel (LoE 1b/A/AGO++) offering a survival benefit of more than 15 months [15]. This dual blockade might also be used in combination with paclitaxel weekly (LoE 2b/B/AGO++) as recently demonstrated [52]. Solvent-free nab-paclitaxel might be another interesting partner for this dual blockade (LoE 3b[a]/C/AGO++) as data from the PERUSE trial demonstrated [53]. These outcome data are superior to those of any other combination of chemotherapy with a single blockade with either trastuzumab or lapatinib in the first-line setting. If chemotherapy is not needed in HER2-overexpressing endocrine-sensitive MBC, the combination of anti-HER2 drugs such as trastuzumab or lapatinib might be recommended together with an AI (LoE 2b/B/AGO+/) (suppl. fig. 3, *www.karger.com/?DOI=477576)*.

Second-Line Treatment in HER2-Overexpressing MBC

The drug conjugate T-DM1 is standard of care after failure of the dual blockade with trastuzumab and pertuzumab (LoE 1b/A/AGO++) and is associated with improved survival [54]. If the patient has not been exposed to a dual horizontal blockade, chemotherapy and dual blockade is an option (LoE 5/D/AGO+/-). A fully oral option is the use of capecitabine and lapatinib (LoE 1b/B/AGO+). In endocrine non-responsive HER2-overexpressing MBC, trastuzumab and lapatinib is recommended as late-line therapy (LoE 2b/B/AGO+).

Specific Sites of Metastasis

Specific sites of breast cancer metastasis are liver, lung, pleura, pericardium, peritoneum, bone marrow, and any soft tissue. Other rare locations such as the adrenals, ovaries, uterus, stomach, colon, or placenta have also been reported; however, in such rare cases, controlled trials are not feasible, and treatment options must be discussed on an individual basis.

Management of primary stage IV breast cancer should focus primarily on systemic therapy, given that the impact of the extent of local treatment on patient survival is still a matter of debate. Although some trials suggested an association between local treatment (surgery or radiotherapy) of the primary tumor and prolonged survival, recent reports do not confirm these observations [55, 56].

Therefore, controversy remains as to i) whether these results reflect a selection of women with good prognosis for primary site therapy; ii) what fraction of women in published studies were diagnosed with metastatic disease just after surgery; iii) whether specific subsets of metastases and biological subtypes would derive greater benefit (e.g. patients with single or few bone metastases [57]); and iv) whether local therapy has been performed appropriately with regard to timing and extent.

If surgery of the primary tumor is performed in the metastatic setting, local excision or mastectomy should be done with tumor-free margins [58, 59]. Axillary surgery is only indicated for bulky disease. Local radiotherapy of the primary tumor can be performed after local surgery according to the indications of the adjuvant setting.

Systemic treatment of metastatic disease is the therapy of choice. Before treatment, metastases should be confirmed by histology to reevaluate the HR and HER2 status. Discordance regarding theses markers may occur in up to 45% of patients and may have 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 favorable factors regarding an improved outcome. Resection of liver metastases is a matter of debate. It may be considered only after histological verification if R0 resection is feasible, no extrahepatic metastases are present, and tumor biology shows a HR-positive breast cancer responding well to former systemic therapy with a long disease-free interval and ≤ 3 metastases [60, 61]. In HER2-positive disease, the age should be < 50 years and the metastasis smaller than 5 cm. In these individual cases, 5-year survival rates of 18–61% can be achieved [62–64]. However, case control studies did not demonstrate a survival benefit for this approach in comparison to systemic treatment alone; therefore, treatment within clinical trials should be preferred [65, 66]. Other procedures like regional radiotherapy, stereotactic body radiosurgery with volumetric intensity-modulated arc therapy, thermoablation, or chemoembolization are also possible in individual cases [67, 68].

For patients with pulmonary metastases, the LoE for a curative approach is low, but some patients might benefit from a metastasectomy followed by appropriate systemic treatment [69, 70]. In accordance with the treatment of liver metastases, resection of lung metastases should only be performed if R0 resection is feasible and histological verification has been done (fine-needle aspiration with CT-guidance or transbronchial needle aspiration). 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 cases, it is the first sign of metastatic disease, resulting in dyspnea and reduced subjective well-being. MPE should be treated in symptomatic cases. To control MPE, thoracoscopy with talcum pleurodesis or povidone-iodine (20 ml of 10% solution) (i.e. video-assisted thoracoscopy, VATS) or continuous pleural drainage with indwelling pleural catheters are options. Some cohort studies and 1 small randomized trial demonstrated a higher efficacy and more activity at 30 days for continuous drainage compared to pleurodesis [71–74]. Less commonly, other sclerosing agents are used (bleomycin, doxycycline, and mitoxantrone) [75]. If the expected lifespan is short, the less invasive procedure should be considered.

Overall, 3% of breast cancer patients will suffer from malignant ascites. Management of ascites takes place in the context of palliative care and aims to improve the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains not recommended [76].

Malignant pericardial effusion and cardiac tamponade remain rare metastatic locations in patients with breast cancer. In symptomatic patients, drainage and pericardial fenestration are probably the best treatment options. For individual patients, VATS or ultrasound-guided puncture with instillation of bleomycin, cisplatin, mitomycin C or mitoxantrone, or bevacizumab may be an alternative [77–81]. A retrospective analysis suggests benefit from the combination of systemic treatment and pericardial drainage [82, 83]. The choice between supportive care or specific anticancer treatment for poor performance status breast cancer patients with multi-metastatic disease and pancytopenia due to bone marrow involvement often remains a clinical dilemma. Aggressive combination regimens have been reported to be effective, since most patients show improved marrow function after chemotherapy, and prolonged survival could be possible. However, in most cases, well tolerated single-agent intravenous weekly treatment (anthracyclines, paclitaxel) or oral capecitabine should be given in order to overcome myelosuppression without endangering the patient's wellbeing. In HER2-positive patients, anti-HER2 treatment should be added [84, 85]. Although endocrine therapy may be feasible in some cases, the urgent need for remission in this life-threatening situation should be taken into account (suppl. fig. 4, *www.karger.com/?DOI=477576).*

Central Nervous System Metastases in Breast Cancer

Metastasis to the central nervous system in breast cancer is of high clinical relevance since the incidence has increased to more than 30% in high-risk groups such as HER2-positive or metastatic TNBC patients [86]. Despite this high incidence, evidence for breast cancer-specific treatment approaches is very limited. Therefore, the AGO Breast Group encourages centers to participate in the German registry for breast cancer patients with brain metastases (*Brain Metastases in Breast Cancer Network Germany*, BMBC) [87]. To guide treatment decisions for breast cancer patients with brain metastases, a diagnosis-specific graded prognostic assessment was developed which takes into account the Karnofsky performance score, biologic subtype, number of brain metastases, and age [88].

Local therapy is the treatment of choice. This can be performed either in the form of whole-brain irradiation (WBRT), stereotactic radiotherapy (radiosurgery or fractionated stereotactic radiotherapy), or surgery. In general, outcome is not improved by surgery compared with radiotherapy. As for most therapeutic options in brain metastases, no breast cancer-specific studies exist. The treatment strategy for patients with limited (1–3, in some studies up to 4) brain metastases is not clearly defined. Indications for surgery could be based on histological verification, e.g. after a long recurrence-free interval, need for immediate decompression in the case of life-threatening symptoms, and tumor size not allowing stereotactic radiotherapy. After surgery, radiotherapy of the resection area is recommended. The integration of WBRT into the treatment plan of patients with a limited number of brain metastases is even less clear. Decline in cognitive function, specifically immediate recall, memory, and verbal fluency, was described to be more frequent with the addition of WBRT to stereotactic radiotherapy. Adjuvant WBRT does not improve overall survival despite better local control. Initial treatment with stereotactic radiotherapy and close monitoring is recommended to better preserve cognitive function in patients with newly diagnosed brain metastases [89] and should even be discussed in patients with multiple brain metastases in which WBRT is still standard of care. With the new radiation technique, conformal avoidance of the hippocampal region, preservation of memory may possibly be improved [90]. In the case of local recurrence in the brain, re-irradiation can be discussed depending on the time interval from first radiation, prior dose, and location.

Systemic therapy in patients with brain metastases in addition to local therapy should be performed as for other metastatic sites. Current systemic therapy may be continued if the patient has a first diagnosis of brain metastases with stable extracranial disease.

In patients with HER2-positive disease, HER2-directed therapy should be continued if remission of extracranial disease is achieved. Retrospective trials show that T-DM1 is also safe in patients with brain metastases [91]. Until now, no newly developed targeted therapy proved to be superior to other agents in the brain. For HER2-positive disease, new tyrosine kinase inhibitors (e.g. ONT-380) are in development, and for HER2-negative disease, new chemotherapeutic options are being developed [92] and will be investigated in upcoming clinical trials.

Supportive Care

In the treatment of hematologic toxicity, the recommendation for the assessment of febrile neutropenia (FN) risk and the prophylactic use of granulocyte-colony stimulating factor in the case of an overall FN risk of ≥ 20% remains unchanged (LoE 1a/A/AGO++). Over the last decade, major concerns were raised regarding the use of erythropoiesis-stimulating agents (ESAs) in the treatment of chemotherapy-induced anemia (CIA). Inconsistent results were reported, especially in the metastatic setting. Leyland-Jones et al. [93] evaluated the impact of epoetin alfa (EPO) on tumor outcomes in 2,098 patients receiving chemotherapy for MBC. Women with hemoglobin ≤ 11.0 g/dl were randomly assigned to EPO 40,000 IU subcutaneously once a week or best standard of care. The primary end point was PFS. Median PFS was 7.4 months in both groups (HR 1.089; 95% CI 0.988–1.200); red blood cell transfusions were 5.8 versus 11.4% ($p < 0.001$), and thrombotic vascular events were 2.8 versus 1.4% ($p = 0.038$) [93].

In the neoadjuvant/metastatic setting, ESA use has an AGO grade of recommendation +/-, and in the treatment of symptomatic CIA in adjuvant chemotherapy of +.

Concerning oral mucositis (OM), prophylaxis is standard of care in all age groups receiving anticancer treatment causing OM (LoE 2b/AGO++). Prevention should consist of regular mouth rinsing (H_2O, NaCl), use of a soft tooth brush, regular cleaning of

the interdental spaces, avoidance of noxious agents, continuous monitoring of lesions, risk-adapted monitoring by a dentist, and close monitoring by the treating oncologist.

Clinically relevant extravasations in the treatment of breast cancer are mainly caused by anthracyclines, taxanes, or vinorelbine. Dexrazoxane is indicated in anthracycline extravasations (LoE 2b/B/AGO++); hyaluronic acid is recommended for treatment of taxane/vinorelbine extravasation (LoE 3b/D/AGO++).

Since the prophylaxis of hand-foot syndrome (HFS) with 5–10% urea-containing creams (10–12×/day) (LoE 1b/AGO+) as well as the prevention of docetaxel-induced paronychia/HFS using cooling gloves (LoE 2b/AGO+) are well established standards, they have been newly integrated into this chapter.

Furthermore, there are new data for scalp cooling and alopecia from a prospective cohort study conducted in 106 patients (scalp cooling) and 16 (control) women with stage I or II breast cancer receiving chemotherapy regimens excluding sequential or combination anthracycline and taxane. Scalp cooling was initiated 30 min prior to each chemotherapy cycle, with the scalp temperature maintained at 3 °C (37 °F) throughout the chemotherapy session and for 90–120 min afterward. Hair loss of 50% or less (Dean score 0–2) was seen in 67/101 (66.3%) patients evaluable for alopecia in the scalp cooling group versus 0/16 (0%) patients in the control group ($p < 0.001$). Of the 106 patients in the scalp cooling group, 4 (3.8%) experienced the adverse event of mild headache, and 3 (2.8%) discontinued scalp cooling due to feeling cold (LoE 1b/AGO+/-) [94].

Peripheral neuropathy is a frequent long-term side effect especially of taxane therapy. According to the recently updated national guideline, AGO recommends physiotherapy/physical therapy (LoE 5/AGO+), duloxetin in the treatment of pain caused by chemotherapy-induced peripheral neuropathy (LoE 1b/AGO+), gapapentin (LoE 1b/AGO+), amitriptyline (LoE 1b/AGO+), venlafaxin (LoE 5/AGO+), and pregabalin (LoE 5/AGO+) [95].

Therapy Side Effects

Acute toxicity and (in most cases) 100-day mortality rates are well documented in the majority of phase III trials. Toxicities are graded according to World Health Organization or National Cancer Institute standards. Various cytotoxic anticancer drugs have their class-specific toxicity profiles. Anthracycline-based standard chemotherapy regimens in the adjuvant setting demonstrate relatively low acute toxicity, and treatment-related mortality rates are below 1%. However, with respect to long-term side effects, cardiotoxicity is clinically relevant. In addition, the impact of the biological age on adjuvant decision-making has to be considered, e.g. by measuring the biological age using the Comprehensive Geriatric Assessment (CGA) [96]. The risk of cardiotoxicity associated with trastuzumab has been reported to be 4% in monotherapy and 27% when administered in combination with anthracyclines and cyclophosphamide; however, life-threatening or severe adverse events are rare [97].

With respect to cardiac toxicity of treatment combinations, see the algorithm in supplemental figure 4 *(www.karger.com/?DOI=477576)* (based on the Affinity/SAKK 2210 study protocol, SAKK = *Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung*, Swiss Oncology Research Network). The combination of pertuzumab and trastuzumab plus docetaxel did not increase the incidence of cardiac adverse events (CLEOPATRA study) [98].

Peripheral sensory neuropathy is a residual side effect. It frequently occurs with taxane-based chemotherapy (grade 1–2 in 20–50%; grade 3–4 in 6–20%). Type of chemotherapy, dose, body mass index, and lack of physical activity are known risk factors for peripheral neuropathy.

Several neuropsychological studies suggest an association between chemotherapy and long-lasting cognitive deficits, possibly related to therapy-induced structural and functional alterations in the brain [99]. Along with the integration of an increasing number of targeted agents into clinical routine, an optimal management of side effects plays an increasingly essential role in the medical treatment of breast cancer.

Non-hematological toxicities such as hypertension (bevacizumab) [100, 101] and stomatitis or pneumonitis (everolimus) [102] are in the focus of several new generations of anticancer drugs.

In the case of CDK4/6 inhibitors, e.g. palbociclib and ribociclib, hematological side effects (neutropenia) are predominant. Unlike chemotherapy, it is mostly grade 1 neutropenia and can be managed by dose reduction without loss of efficacy.

An adequate knowledge of the class-specific toxicity profiles should be mandatory for every oncologist working in this field. First of all, close monitoring of such patients is necessary, because early intervention is often indicated in the case of drug-related symptoms. For the new class of immunomodulators, new toxicities like hepatitis, colitis, nephritis, pneumonitis, and hypophysitis can occur, and knowledge with regard to the recognition and management of these conditions is very important.

Summary

Advanced breast cancer is a systemic disease. The primary goal of treatment is to control the disease and maintain or even improve quality of life. In ER-positive advanced breast cancer patients, endocrine treatment is a mainstay of therapy unless there is rapidly progressive life-threatening disease. In addition to endocrine therapy, newer agents like palbociclib or everolimus can further improve PFS. In HER2-positive patients, dual blockade with trastuzumab/pertuzumab and, in later lines, the antibody-drug conjugate T-DM1 are effective therapeutic options extending survival with preserved quality of life. Chemotherapy (e.g. taxanes, anthracyclines, capecitabine) can be used to control resistant and/or rapidly progressive disease. Bearing in mind that quality of life is essential, adequate management of toxicities and side effects is mandatory. Furthermore, bone-modifying agents like BP or denosumab are crucial in the treatment of bone metastases. In addition to these

systemic treatment options, local therapies like radiotherapy or surgery might be considered (e.g. bone or brain metastases). Despite these unquestionable treatment advances, advanced breast cancer remains a disease which is essentially incurable. Taking this into account, combined standard oncology care and palliative care should be considered early in the course of the illness.

Online Supplemental Material

Suppl. fig. 1. Follow-up care for breast cancer.

Suppl. fig. 2. Treatment recommendations for postmenopausal patients with metastatic breast cancer.

Suppl. fig. 3. Treatment recommendations for first-line treatment of HER2-positive metastatic breast cancer.

Suppl. fig. 4. General aspects of surgery or ablation of metastases.

To access the supplemental material please refer to *www.karger.com/?DOI=477576.*

References

References can be found in the appendix; please refer to *www.karger.com/?DOI=477576.*

Disclosure Statement

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