AGO Recommendations for the Diagnosis and Treatment of Patients with Advanced and Metastatic Breast Cancer: Update 2018

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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. 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.

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ogy. This update was performed according to a documented rule-fixed algorithm, 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 (GR); suppl. table 1). We here-with present the 2018 update; the full version of the updated slide set is available online as a portable document format (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 Osteo-Oncology

Bone Metastasis

Osteoclast-inhibiting therapy including denosumab and bisphosphonates (BPs) for reducing the risk of skeletal complications is the standard treatment for breast cancer patients with bone metastases. The approved schedule for denosumab (120 mg subcutaneously (s.c.)) is every 3–4 weeks. Since 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, the administration of zoledronic acid q12w (LoE 1a/A/AGO++) should be preferred over zoledronic acid q4w (LoE 1a/A/AGO+). As a new rare side effect, inflammatory eye reactions with BPs have been reported [3]. Based on these observations, patients with eye problems should be referred to an ophthalmologist (LoE 4). Osteoclast-inhibiting therapies alone are not sufficient to overcome pain associated with bone metastases (LoE 5/D/AGO–). Therefore, additional pain management is mandatory including radiotherapy

and analgesic drugs [4]. Radiotherapy can be combined with hyperthermia to increase the efficacy of treatment (LoE 2b/B/AGO+/-) [5]. The measurement of bone resorption markers to monitor therapy response is not recommended due to conflicting results (LoE 5/D/AGO-) [4].

Bone Health

Bone health is an important issue for breast cancer patients during follow-up. The risk assessment for osteoporosis should be performed in every patient to identify those eligible for additional measures. Patients treated with aromatase inhibitors (AIs) or suffering from premature ovarian failure should receive an initial bone mineral density (BMD) measurement. The only validated method of choice is the dual-energy X-ray absorptiometry (DXA) test. The intervals of BMD measurements are based on individual risk and treatment (LoE 5/D/AGO+) [6–8]. Denosumab and BPs are the standard treatment for the prevention and therapy of osteoporosis. Recent studies indicate that discontinuation of denosumab may increase the risk of vertebral fractures. Therefore, continuation of treatment with other antiresorptive drugs should be considered [9, 10].

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).

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 and 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 adherence (especially to endocrine therapy (ET)) is an essential part of follow-up care (LoE 2b/B/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, fat-reduced diet, reduced alcohol consumption, physical activity, nightly fasting, distress reduction) and interventions with regard to comorbidities (diabetes) are further important aspects of follow-up.

From the patient's perspective, examination of the breast, reassurance, guidance and answering questions, evaluation of treatment including side effects, and psychosocial support are also essential.

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 (PET) scans, and monitoring of circulating tumor cells (CTCs). For the detection of curable events, self-examination and physical examination in combination with mammography and adjunctive ultrasound are recommended.

In case of increased risk such as age <50 years, hormone receptor (HR) negativity, and decreased diagnostic accessibility C/D in mammography and ultrasound, magnetic resonance imaging should be considered [102].

In this context, screening for second malignancies according to guidelines (e.g., colorectal, endometrial, ovarian cervical cancer, lymphoma) is meaningful. Further, a DXA scan at baseline and a repeat scan according to individual risk in women with premature ovarian failure or in women on AI therapy are recommended [11].

Locoregional Recurrence

In patients with locoregional relapse, pretherapeutic biopsy to re-assess histology as well as the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status is strongly recommended (LoE 3b/B/AGO++) [12]. 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 the time of onset of obesity. This was shown in a recent meta-analysis of 82 studies (n = 213,075) (LoE 1a) [13]. 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 [14, 15]. 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 (LoE 2a/B/AGO-) [16].

Axillary dissection should not be performed in cases with cN0 disease. With regard to systemic therapy, the CALOR trial (n = 162; median follow-up 9 years) demonstrated a significant benefit for postoperative chemotherapy in patients with fully excised isolated locoregional recurrence (ILRR), particularly in cases with ER-negative disease (LoE 2b/B/AGO+). Hazard ratios (HRs) of a disease-free survival (DFS) event were 0.29 (95% confidence interval (CI) 0.13–0.67) in patients with ER-negative and 1.07 (95% CI 0.57–2.00) in patients with ER-positive ILRR ($P_{\text{interaction}} = 0.013$). The authors concluded that the final results confirm that CT benefits patients with resected ER-negative ILRR and does not support the use of CT for ER-positive ILRR [17].

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 [18]. 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 ($\pm$ hyperthermia) may be discussed (LoE 3a/C/AGO+/-). However, these patients seem to have an unfavorable prognosis [19].

Endocrine and Targeted Therapy in Metastatic Breast Cancer

In women with HR-positive metastatic breast cancer (mBC; HER2-negative), endocrine-based therapy should be considered, irrespective of the menopausal symptoms. Premenopausal women rendered postmenopausal by either gonadotropin-releasing hormone (GnRH) analogues or other means of ovarian function suppression should then be treated as postmenopausal women.

The majority of patients might be candidates for a cyclin-dependent kinase 4/6 (CDK4/6) inhibitor combination therapy. Palbociclib and ribociclib (LoE 1b/B/AGO++) seem to have a slightly better benefit risk profile than abemaciclib (LoE 1b/B/AGO+). But all 3 drugs have been thoroughly investigated in first and further lines in endocrine-sensitive and -resistant mBC and demonstrated a homogeneous HR between 0.42 and 0.58. So far, no subgroup could be identified neither by clinical nor by biomarkers that does not benefit from using a CDK4/6 inhibitor in addition to ET [20–23]. In premenopausal (suppl. fig. 2) women, the recommendations are identical to those given for postmenopausal (suppl. fig. 3) women following the general recommendations, although only the MONALEESA-7 trial using ribociclib was conducted in premenopausal women (LoE 1b/B/AGO++), whereas in PALOMA-3 (further line) and MONARCH-2 about 20% premenopausal women were included (LoE 2b/B/AGO++) [20–24].

Patients carrying a germline BRCA mutation might be candidates for poly(ADP-ribose) polymerase (PARP) inhibitors. While the OlympiAD study using olaparib demonstrated a significant benefit only for TNBC patients [25], the EMBRACA study using talazoparib showed an equal benefit for patients with HR-positive and -negative HER2-negative mBC patients who have received up to 2 lines of previous therapy [26]. Currently, the recommendation is therefore stronger for TNBC patients to be treated with olaparib instead of chemotherapy in germline BRCA mutation carriers.

All other recommendations have not changed and remain valid.

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, rebiopsy of metastatic lesions is recommended to optimize treatment decisions using the infor-

mation of the phenotype determined at 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) [12].

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 ET is likely (LoE 1a/A/AGO++). A clinically meaningful remission during cytotoxic treatment suggests continuation of this treatment option (LoE 1b/A/AGO++). HER2/neu overexpression is a predictive marker for anti-HER2-directed drugs (LoE 1a/A/AGO++). In case of bone metastases, bone-modifying drugs should be used (LoE 1b/A/AGO+) [12]. CTCs to monitor remission or progression of mBC might be a useful parameter in the setting of a well-designed clinical trial (LoE 1b/A/AGO+). Outside of this setting, CTCs should be used with caution [27].

Treatment in mBC – General Considerations

In mBC, we should be aware of the patients' preferences and expectations and discuss with them the rationale of the different treatment options. If chemotherapy is indicated, we have to re-evaluate remaining toxicities from previous treatment lines, the treatment-free interval (e.g., time since the end of adjuvant therapies), the localization 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 given patient. It might be helpful to have a realistic estimation of the remaining life time (AGO++) [28].

Primary and Secondary Endocrine Resistance

ET is the mainstay of targeted therapy in endocrine-sensitive mBC (LoE 1a/A/AGO++). In case of progression, we have to differentiate between *primary endocrine resistance*, defined as treatment failure while on adjuvant ET within the first 2 years or within the first 6 months of first-line ET for mBC, and *secondary endocrine resistance* if progression occurs after the first 2 years of adjuvant ET or, in mBC, if progression is detected after the first 6 months of treatment [12]. In endocrine-sensitive mBC, the introduction of ET is recommended as long as no life-threatening metastases are diagnosed (AGO++).

Chemotherapy in mBC

If chemotherapy is indicated in mBC, the use of monotherapy is recommended over a combination chemotherapy as long as the therapeutic index is better (LoE 1a/A/AGO++) [12]. Assuming a positive therapeutic index, the preferred option is to treat until progression (LoE 2b/B/AGO+), rather than 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 case of progressive disease or intolerable toxicity (LoE 1c/A/AGO++) [29]. Compliance and adherence to any treatment in mBC, as well as performance status, toxicity, and clinical symptoms including the target

lesion, should be re-evaluated on a regular basis every 2 months or every 2–4 cycles, whatever is clinically reasonable (LoE 1a/A/AGO++) [30].

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

After pretreatment with anthracyclines, the first options are taxanes, preferably using weekly paclitaxel (LoE 1a/A/AGO++) or docetaxel every 3 weeks (LoE 1a/A/AGO++) [31]. Nanoparticle albumin-bound (nab)-paclitaxel as weekly or 3-weekly schedule is an alternative option (LoE 2b/B/AGO++) [32]. Capecitabine, an oral cytostatic that does not cause alopecia, is another available option (LoE 2b/B/AGO++). In addition, liposomal doxorubicin (LoE 2b/B/AGO+), eribulin (LoE 1b/B/AGO+), and vinorelbine (LoE 2b/B/AGO+) are further available cytostatic drugs.

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

Patients at high risk of recurrence are exposed to anthracyclines and taxanes either in the neoadjuvant or the adjuvant setting. In case of relapse, participation in clinical trials is recommended (AGO++). In clinical routine, capecitabine is the treatment of choice in the first-line setting (LoE 2b/B/AGO++). Alternative drugs for use as monotherapy are eribulin (LoE 1b/B/AGO++) or vinorelbine (LoE 2b/B/AGO++) [33]. When a rechallenge of previously given drugs is indicated, taxane rechallenge should not be performed within 12 months after the last taxane application (LoE 2b/B/AGO+) [34]. Liposomal doxorubicin might be used in the same indications (LoE 2b/B/AGO+). In asymptomatic patients, a low-dose metronomic chemotherapy is a reasonable option in heavily pretreated patients (LoE 2b/B/AGO+). If the patient is heavily symptomatic and the use of combination chemotherapy is indicated, gemcitabine either in combination with platinum salts (LoE 2b/B/AGO+/-) or with capecitabine (LoE 2b/B/AGO+/-) might be an option [35, 36]. In contrast, the data does not recommend the combination of gemcitabine and vinorelbine (LoE 1b/B/AGO-).

Management of Triple-Negative mBC (TNBC)

Most patients are pretreated with anthracyclines and taxanes in early breast cancer. At relapse, 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+) [37]. Carboplatin might also be given in combination with gemcitabine (LoE 1b/A/AGO+) or in combination with nab-paclitaxel (LoE 2b^a/B/AGO+) [38].

Management of BRCA1/2 Mutation Carriers

The aforementioned phase III TNT trial was the first trial with a priori planned subgroup analyses in *BRCA1/2*-mutated breast cancer and the basal-like subtype. In an unselected triple-negative mBC population, the use of either docetaxel (100 mg/m² q3w) or carboplatin (area under the curve (AUC) = 6 q3w) demonstrated similar efficacy. In *BRCA1*- or -2-mutated breast cancer, the plati-

num was superior in terms of response rate and time to progression (6.8 vs. 3.1 months). The first randomized phase III trial that compared olaparib monotherapy with single-agent chemotherapy in HER2-negative patients with a germline *BRCA* mutation has been published [39]. Patients had received no more than 2 previous chemotherapy regimens for metastatic disease. The median progression-free survival (PFS) was significantly longer in the olaparib group than in the standard therapy group (7.0 vs. 4.2 months). The HR for disease progression or death was 0.58 ($p < 0.001$). Thus, olaparib provided a significant benefit over the physician's choice (capecitabine, eribulin, or vinorelbine in 21-day cycles).

Bevacizumab in the Management of HER2-Negative mBC

Bevacizumab is used as a targeted drug without evaluation of the target itself [40, 41]. 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+). Data from the IMELDA trial suggests the use of capecitabine and bevacizumab as maintenance therapy in patients with complete remission (CR), partial response (PR), or stable disease (SD) after induction therapy with doxorubicin and bevacizumab. This sequential approach is improving survival compared to bevacizumab alone [42, 43]. 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 the TANIA trial revealed that continuing bevacizumab beyond the first and second progression of locoregional recurrence/mBC improved the second-line PFS, but no improvement in longer-term efficacy was observed [44].

First-Line Treatment in HER2-Positive mBC

In HER2-positive mBC, standard of care is the dual horizontal blockade of the HER2 receptor by trastuzumab and pertuzumab in combination with docetaxel (LoE 1b/A/AGO++), offering a survival benefit of more than 15 months [45]. This dual blockade might also be used in combination with paclitaxel weekly (LoE 2b/B/AGO++) (suppl. fig. 4), as recently demonstrated [46]. Solvent-free nab-paclitaxel might be another interesting partner for this dual blockade (LoE 3b^a/C/AGO++) as suggested by data from the PERUSE trial [47]. Summarizing, the outcomes of dual blockade are definitely superior to any other combination of chemotherapy with single blockade with either trastuzumab or lapatinib in the first-line setting. If chemotherapy is not needed in HER2-positive endocrine-sensitive mBC, the combination of anti-HER2 drugs such as trastuzumab or lapatinib might be recommended in combination with AIs (LoE 2b/B/AGO+/-).

Second-Line Treatment in HER2-Overexpressing mBC

The drug conjugate T-DM1 (trastuzumab-emtansine) is standard of care after failure of trastuzumab and is associated with improved survival (LoE 1b/A/AGO++) [48]. No data for patients pretreated with today's standard of dual blockade with trastuzumab and pertuzumab in the first-line setting of mBC is available. How-

ever, T-DM1 is an option in this clinical situation. If the patient has not been exposed to a dual horizontal blockade in the first line, chemotherapy and dual blockade is an option (LoE 5/D/AGO+/-). After progression, continuing trastuzumab and switching to a different chemotherapy like capecitabine is still an option (LoE 2b/B/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 Metastases

Specific sites of breast cancer metastases are liver, lung, pleura, pericardium, peritoneum, bone marrow, or any soft tissue. Other rare localizations like 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. Surgical treatment should be considered on an individual basis as it does not seem to influence overall survival [49]. Only in women with limited metastatic disease and a good response to systemic treatment, surgical procedures at the primary as well as the metastatic site should be taken into account [50–52].

If surgery of the primary tumor is performed in the metastatic setting, local excision or mastectomy should be done resulting in free margins [53]. Axillary surgery is only indicated for bulky disease. Local radiotherapy of the primary tumor can be performed after local surgical treatment 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 re-evaluate the HR and HER2 status. Discordance regarding these 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 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, if no extrahepatic metastases are present, and if the tumor biology shows an HR-positive breast cancer responding well to former systemic therapy with a long disease-free interval and ≤ 3 metastases [54, 55]. 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 [56–58]. However, case-control studies did not demonstrate a survival benefit by this approach in comparison to systemic treatment alone; therefore, treatment within clinical trials should be preferred [59, 60]. Other procedures like regional radiotherapy, stereotactic body radiosurgery with volumetric intensity-modulated arc therapy, thermoablation or chemobolization are also possible in individual cases [61, 62].

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 [63, 64]. In accordance with the treatment of liver metastases, resection of lung metastases should only be performed if R0 resection is feasible and histological verification was 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. It should be treated in symptomatic cases. To control MPE, thoracoscopy with talcum pleurodesis or povidone-iodine (20 ml of a 10% solution) (i.e., video-assisted thoracoscopy (VATS)) or continuous pleural drainage with indwelling pleural catheters are options of choice. Some cohort studies and 1 small randomized trial demonstrated a higher efficacy and more activities at 30 days in continuous drainage compared to pleurodesis [65–69]. More rarely, other sclerosing agents are used (bleomycin, doxycycline, and mitoxantrone) [70]. If the expected life span 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 at improving the quality of life of these patients. Patients with symptomatic ascites should undergo drainage. Local antibody therapy with catumaxomab remains not recommended [71].

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 treatment options of choice. For individual patients, VATS or ultrasound-guided puncture with instillation of bleomycin, cisplatin, mitomycin C, or mitoxantrone, or bevacizumab may be an alternative [72–74]. A retrospective analysis suggests benefit from the combination of systemic treatment and pericardial drainage [75, 76]. It has been reported that aggressive combination treatment regimens were effective, since most patients showed 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 well-being. In HER2-positive patients, anti-HER2 treatment should be added [77, 78]. Although ET may be feasible in some cases, the urgent need for remission in this life-threatening situation should be taken into account.

Therapy Side Effects and Supportive Care

In order to harmonize both, the topic of side effects and supportive care were merged to one topic in this issue of the AGO recommendations. Most of the recent recommendations of supportive care are well described in the recently published German S3 guide-

line [79]. Nonetheless, in breast cancer care, acute and delayed toxicities should be monitored in a regular way. For acute toxicities, the well-established National Cancer Institute Common Toxicity Criteria (NCI-CTC) grades should be used (LoE 5/D/AGO++) [80]. Long-term toxicities correspond to secondary diseases after tumor therapy and should also be detected and documented (e.g. using the International Classification of Primary Care (ICPC) symptom list or the International Classification of Diseases 10 German Modification (ICD-10-GM) list of diagnoses; LoE 5/D/AGO++) [81–83]. Details on therapy side effects and recommendations on incidence, prevention, and management are depicted according to the MedDRA system organ classes (Medical Dictionary for Regulatory Activities). Using the information that is provided by the respective manufacturer's technical product information [84], incidences of side effects of the common compounds of chemotherapy and ET are listed; important side effects are emphasized.

The standards with regard to treatment-related blood disorders (anemia, neutropenia) have not been changed. Details of progress in antiemetic prevention and treatment are well documented in the updated American Society of Clinical Oncology (ASCO) guideline [85]. It should be pointed out that if traditional regimens fail to prevent nausea and emesis, rescue medication as olanzapine, levomepromazine, benzodiazepines, cannabinoids, or ginger should be considered (LoE 3b/C/AGO+).

Before starting chemotherapy or immune-suppressive treatment, hepatitis B virus screening is recommended by determining serum levels of HBsAG and anti-HBC (LoE 2/C/AGO+). Reactivation of chronic hepatitis B can be fatal, facing mortality up to 30%. In addition, reactivation of hepatitis B might also impair the cancer treatment (e.g. by delaying chemotherapy), thus potentially also enhancing the breast cancer-specific mortality. With a prevalence of about 1:100 in the general German population and having effective virustatic treatment options, an early detection of chronic hepatitis B is cost effective [86–88]. This recommendation by the Infectious Diseases Working Party (AGIHO) of the German Society for Hematology and Medical Oncology (DGHO) is in line with other European and further international guidelines. Of course, in case of positive serology or clinical reactivation, chemotherapy has to be stopped and specific antiviral therapy should be started in cooperation with a hepatologist (suppl. fig. 5).

Taxanes are standard in most adjuvant and many palliative therapies. Thus, chemotherapy-induced peripheral neuropathy (CIPN) is an increasing problem. Special emphasis has to be pointed to prevention, since effective treatment is not known. There is no evidence for an effective drug-based prevention of CIPN, but particularly physical measures seem to be helpful. Functional training including sensomotoric stimulation is recommended (LoE 5/D/AGO+). In addition, there is evidence from 1 trial that compression therapy for hands (and feet) might be effective in reducing particularly the risk of intermediate and severe neuropathy [89–91]. Patients should wear tight surgical latex gloves (even double) on each hand (and tight stockings) during taxane infusion (LoE 2b/B/AGO+). However, with regard to treat-

ment beside sensomotoric stimulation and physiotherapy (LoE 2b/C/AGO+), pharmaceutical interventions should be tried. Locally administered menthol preparations can be a first step that is well accepted by many patients (LoE 5/D/AGO+). Also local application of a special mixture of baclofen/ketamine/amitriptylin has been shown to mitigate neuropathic complaints (LoE 2b/B/AGO+). Best evidence exists for systemic duloxetine treatment; however, patients sometimes do not tolerate the side effects (LoE 1b/B/AGO+). Finally, also opioids can be used to control neuropathic pain. A list of recommended and not recommended interventions can be found in the very detailed ASCO guidelines published by Hershman et al. [92] in 2014. There is no evidence of a beneficial effect of vitamins or phytotherapies with regard to prevention or therapy of CIPN.

Cardiotoxicity is of major concern in a variety of drugs; however, it is pronounced if anthracyclines or trastuzumab are used. There is no real difference of cardiac side effects between epirubicin and doxorubicin in the recommended cumulative doses (LoE 2b/B), but at least for liposome-encapsulated doxorubicin less cardiotoxicity has been evaluated (LoE 1b/B). Unfortunately, there is only scarce data about the adjuvant use of this drug. Anthracycline- or trastuzumab-associated cardiotoxicity may occur earlier and more frequently if cardiac risk factors are present, as in elderly patients and in case of obesity, hypertension, hypercholesterolemia, pre-existing cardiac diseases (including borderline left ventricular ejection fraction (LVEF)), and diabetes mellitus. Although 1 study showed a protective effect of prophylactic beta-blocker treatment during anthracycline therapy, there is no proven and commonly accepted pharmaceutical prevention (LoE 2a/B/AGO+/-) [93]. However, regular and standardized monitoring of cardiac function using echocardiography (LVEF or shortening fraction (SF) in %) is recommended (LoE 3b/C/AGO+).

Drug-induced alopecia is an issue of quality of life in all cancer patients. 2 trials demonstrated effectiveness of scalp cooling with modern devices, resulting in 50% reduction of chemotherapy-induced alopecia (maybe particularly in taxane-based chemotherapy). More data are required with regard to safety and patient acceptance before it can generally be recommended (LoE 2b/B/AGO+/-) [94].

Side effects of targeted drugs should increasingly be considered, since failure of their management can preclude the use of potentially effective drugs.

Everolimus is frequently accompanied by any grade of mucositis (67% in the BOLERO-2 study). A recently published single-arm phase II study (SWISH) demonstrated that regular mouth washings with a dexamethasone solution (in addition to the generally recommended mouth hygiene) can significantly reduce the rate of everolimus-induced mucositis compared to historical data from BOLERO-2 (after 13 weeks grade ≥ 2 events 9% vs. 27%) [95]. With increasing use of CDK4/6 inhibitors, specific toxicities have to be recognized. Severe neutropenia can be observed regularly and has to be managed; however, it is pronounced in palbociclib (all grades 80.6%) and ribociclib (74.2%) treatment. Particularly with abemaciclib therapy (86.4%), any grade of diarrhea is observed in

nearly every patient and must be managed prospectively. Mild alopecia is seen in 15–35% of all CDK4/6 inhibitor patients [22, 23, 96].

With ribociclib, attention has to be given to QT interval prolongation (6.9% > 480 ms; 1.5% > 500 ms). QT interval prolongation is not necessarily associated with symptoms; however, QT interval prolongation stands for an elevated risk of life-threatening arrhythmia ‘torsades de pointes’ (TdP). Thus, electrocardiography (ECG) monitoring during ribociclib therapy is recommended according to the manufacturer’s technical product information.

PARP inhibitors (e.g., olaparib, talazoparib) rather frequently show a wide range of side effects (nausea, emesis, fatigue, diarrhea, pyrexia, cough, etc.); however, severe-grade toxicities were seen only with regard to neutropenia and anemia [97] (suppl. fig. 6).

The use of inhibitors of receptor tyrosine kinases is limited by the frequent occurrence of severe diarrhea (any grade/grade $\geq$ 3: lapatinib 61%/6%, neratinib 95%/40%). Thus, primary prophylactic use of loperamide is recommended particularly with neratinib (LoE 2b/B/AGO++) [98, 99].

With regard to the upcoming immune checkpoint inhibitors (iCPI), new toxicities must be kept in mind. Particularly autoimmune phenomena have to be managed. Nearly every organ can be involved. There are drug-specific different time intervals from the start of therapy; e.g., with nivolumab, rash is often seen after 2 weeks, hepatitis after 3 weeks, hypothyroidism after 4 weeks, but pneumonitis as late as 10 weeks and later. Also iCPI toxicities have to be graded (e.g. according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE)) and monitored. With grade-1 reaction, supportive care, close monitoring, exclusion of acute infections and information together with a close follow-up of the patient are sufficient. However, with grade-2 toxicity and higher, discontinuation of treatment is mandatory, and corticosteroid treatment and, in higher grades, even intensified immunosuppressive therapy is required. Details were recently published in the very comprehensive ASCO guidelines [100].

References

References can be found in the appendix; please refer to www.karger.com/?DOI=489331.

Palliative Care

It is well accepted that mBC is incurable but treatable. Early introduction of palliative care concurrent with active treatment is important to improve symptoms and quality of life. Furthermore, discussions about patient preferences at the end of life should begin early in the course of metastatic disease [12, 101].

Online Supplemental Material

Suppl. table 1. AGO grades of recommendation.

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

Suppl. fig. 2. Endocrine-based treatment options in premenopausal patients with HER2-negative metastatic breast cancer.

Suppl. fig. 3. Endocrine-based treatment options for postmenopausal patients with HER2-negative metastatic breast cancer.

Suppl. fig. 4. First-line therapy of HER2-overexpressing metastatic breast cancer.

Suppl. fig. 5. AGIHO/DGHO recommendations on hepatitis B virus screening in oncology.

Suppl. fig. 6. Toxicities of PARP inhibitors – olaparib and talazoparib.

To access the supplemental material please refer to www.karger.com/?DOI=489331.

Disclosure Statement

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