Third consensus on medical treatment of metastatic breast cancer


1Institute of Oncology, Sarajevo, Bosnia and Herzegovina; 2Centre Oscar Lambret, Lille, France; 3Dana-Farber Cancer Institute, Boston, MA, USA; 4Oncologisch Centrum, Universitair Ziekenhuis, Gent, Belgium; 5Department of Surgery, Medical University of Vienna, Vienna, Austria; 6Medizinische Klinik und Poliklinik III Klinikum Gießhaiden, Munich, Germany; 7Department of Oncology and Radiotherapy, Medical University, Gdansk, Poland; 8Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Vienna, Austria; 9Istituto Tumori, Milan, Italy; 10Centre Paul Strauss, Strasbourg, France; 11Department of Oncology, Charles University, Prague, Czech Republic; 12Medizinische Klinik der Charite, Berlin, Germany; 13Charing Cross Hospital, Imperial College, London, UK; 14University of Pennsylvania Cancer Center, Philadelphia, PA, USA; 15Sydney Cancer Centre, Royal Prince Alfred Hospital and Concord Hospitals, University of Sydney, Camperdown, Sydney, New South Wales, Australia; 16Breast Cancer for Aptium Oncology at Lynn Cancer Institute-West, Boca Raton, FL, USA; 17Department of Medical Oncology and Palliative Care, Westmead Hospital, Sydney, Australia; 18Central European Cooperative Oncology Group, Vienna, Austria and 19Department of Medicine I, Medical University of Innsbruck, Austria

Received 17 February 2009; revised 23 March 2009; accepted 30 March 2009

Background: Treatment options for patients with metastatic breast cancer (MBC) include a rapidly expanding repertoire of medical, surgical and supportive care measures.

Design: To provide timely and evidence-based recommendations for the diagnostic workup and treatment of patients with MBC, an international expert panel reviewed and discussed the evidence available from clinical trials regarding diagnostic, therapeutic and supportive measures with emphasis on their impact on the quality of life and overall survival of patients with MBC.

Results: Evidence-based recommendations for the diagnostic workup, endocrine therapy, chemotherapy, use of targeted therapies and bisphosphonates, surgical treatment and supportive care measures in the management of patients with MBC were formulated.

Conclusions: The present consensus manuscript updates evidence-based recommendations for state-of-the-art treatment of MBC depending on disease-associated and biological variables.

Key words: diagnosis, metastatic breast cancer, prognosis, treatment

introduction

Breast cancer is the most common malignancy among women in the developed countries. Although impressive improvements have been made in the adjuvant treatment of early breast cancer, ~20% of patients initially diagnosed with regional stage disease will develop metastatic breast cancer (MBC) [1, 2]. The medical treatment of MBC offers a wide range of options including chemotherapy, endocrine treatment, therapy with antibodies directed against growth factors relevant to the disease, tyrosine kinase inhibitors (TKIs) and supportive measures. The abundance of treatment options has contributed to an impressive amelioration of prognosis in a proportion of patients with MBC [1]. In contrast to a series of very relevant consensus statements and recommendations on adjuvant treatment of early breast cancer [3–6], only very few similar initiatives have been undertaken to generate a consensus on the medical treatment of MBC [7] with the one generated by the Central European Cooperative Oncology Group (CECOG) ranking among the first [8]. The second CECOG consensus on the medical treatment of MBC was published only in 2007 [9]. Since then, a series of important new drugs have been successfully brought to the market, and some well-known drugs have been further developed in clinical trials necessitating an update of treatment recommendations within an interval of 2 years.

The current consensus on the medical treatment of MBC continues the tradition of previous similar publications by CECOG [8–10] in that all participants had to agree upon its content and evidence-based recommendations for state-of
the-art treatment, considering available treatment options in relation to various clinical and biological variables.

Encouraged by previous considerations and recent data, the panel agreed to hold up its previous statement [9] that the primary goals of treatment in MBC include

- maximizing the quality of life (QoL),
- prevention and palliation of symptoms and
- prolongation of survival

Concordant with the previous recommendation [9] and due to the biological variability of the patient and her disease, the decision for the optimal timing of treatment initiation and the continuation of treatment has to be made on an individual basis.

Treatment choices for MBC are guided by

- hormone receptor [estrogen receptor (ER) and progesterone receptor (PgR)] status of the primary tumor or its metastases,
- HER-2/neu status,
- the duration of the relapse-free interval since primary diagnosis and since completion of adjuvant therapy for breast cancer,
- the location and extent of metastases (visceral versus nonvisceral),
- previous treatment (including its effects and tolerance),
- patient symptoms,
- patient preferences,
- anticipated side-effects of treatment and
- the availability and access to treatment

methods of consensus formation

panel composition

The CECOG has invited an expert panel consisting of experts in clinical medicine (i.e. medical oncology, radiotherapy and surgical oncology) and clinical and translational research with a focus on expertise in breast cancer to examine evidence focused upon medical treatment of MBC. In doing so, experts were asked to consider previous recommendations made by the group in preceding years [8, 9] and to put them into perspective with recent data, with special emphasis upon their impact on clinical practice. The panel participants were from Australia, Europe and the United States.

literature review and analysis

In accordance with previous reports [8, 9], MBC was defined according to the tumor–node–metastasis system classification (6th edition) of the American Joint Committee on Cancer [11] as any T, any N, M1 tumor of the breast. Similar to previous publications, the present recommendations of the consensus panel concern patients with stage IV disease.

In analogy to our methods, electronic and manual searches including Medline and The Cochrane Library (search terms: breast cancer, metastatic and clinical trial) and abstracts published in the proceedings of major international oncology meetings including conferences of the American Society of Clinical Oncology, the San Antonio Breast Cancer Symposium, the European Conference of Clinical Oncology, the European Society of Medical Oncology and the European Breast Cancer Conference were used for identifying relevant literature. Articles or abstracts were selected for inclusion to a systematic review of the literature on the management of patients with MBC if they represented randomized controlled trials (RCTs) with appropriate control groups or meta-analyses of RCTs in patients with stage IV breast cancer. Data from phase II clinical trials or retrospective analyses were included only in case of lack of evidence from randomized phase III clinical trials. As mentioned above, the main goals of treatment in patients with MBC include prevention and palliation of symptoms, maximizing the QoL and prolongation of survival. However, like in previous reports [8, 9], the panel recognized that most randomized clinical trials enrolling patients with MBC were not designed to provide a quantitative comparison of differences in survival adjusted by the concomitant changes in QoL, i.e. to measure differences in quality-adjusted life years. Thus, the panels agreed that for consensus formation regarding therapies targeting the tumors, overall survival (OS) should be the primary outcome of interest and that significant differences in QoL or toxicity between interventions should be indicated. In contrast, differences in QoL were the primary outcome of interest for supportive care interventions. Progression-free survival (PFS) and response rates (RRs) or disease stabilization were considered as secondary outcomes.

consensus formation

The panel formed subcommittees of two to six participants. Each subcommittee was assigned a coordinator and independently reviewed publications addressing particular aspects relating to the medical management of MBC including (i) endocrine treatment, (ii) cytotoxic therapy, (iii) treatment of Her-2/neu-overexpressing MBC, (iv) bisphosphonates, (v) supportive care, (vi) surgery, (vii) high-dose therapy and (viii) future directions.

Each subcommittee independently reviewed and summarized the data available until December 2008 from articles published in peer-reviewed medical journals and abstracts presented at international cancer conferences for the assigned aspect in the management of MBC. Each subcommittee presented a consensus proposal. Recommendations of the consensus panel represent statements that all members of the panel agreed upon.

All members of the panel participated in the preparation of a draft guideline document, which was then repeatedly disseminated for review by the entire panel. Final text editing was completed by CCZ and WJK and accepted by all panelists.

diagnosis of MBC and assessment of biological variables

The panel continued to agree that histological or cytological verification of metastatic disease is not required routinely, although a biopsy of a metastatic lesion may be advisable to confirm the presence of metastatic tumor (if there is ambiguity) and to characterize the biological markers associated with tumor recurrence including the reassessment of the ER and PgR status by standardized immunohistochemistry (IHC) and of Her-2/neu status by IHC or FISH.

Diagnostic imaging workup should include assessment of frequent sites of metastases including the lung, liver and bone. In addition, radiological imaging of the central nervous system (CNS) should be considered in Her-2/neu-positive patients [12].

recommendations for the assessment of steroid receptor expression

Standardized testing and quality control of steroid receptor determination remains to be mandatory due to the discordance rate between local and central laboratory testing for ER and PgR [13, 14]. Expression of ER and PgR should be reported in a semiquantified way (e.g. by using the Allred score).
recommendations for the assessment of Her-2/neu protein overexpression and gene amplification

Her-2/neu status should be assessed by IHC, FISH or chromogenic in situ hybridization (CISH). When carried out in central laboratories with appropriate expertise, the level of concordance between Her-2/neu 3+ overexpression assessed by IHC and FISH or CISH is high [15–17]. Results of 3+ IHC or FISH positivity in high-volume laboratories continue to be the gold standard for the detection of Her-2/neu positivity. In tumors with 2+ protein overexpression by IHC, FISH testing should be carried out for the decision on an indication for treatment with Her-2/neu-directed therapies such as trastuzumab and lapatinib [18, 19]. The panel repeated previous recommendations that efforts to standardize testing for Her-2/neu overexpression should be strongly encouraged. For IHC, Her-2/neu testing should be carried out by a standardized assay and scoring system according to the manufacturer’s recommendations (HercepTest®, DAKO Inc., Glostrup, Denmark) [18].

Data indicating a benefit for trastuzumab in the adjuvant setting for patients who have neither overexpression by IHC nor gene amplification by FISH should be considered as hypothesis generating [20] in the light of results of the CALBG 9840 trial which failed to demonstrate any apparent clinical benefit of trastuzumab in patients with Her-2/neu-negative MBC receiving first-line paclitaxel chemotherapy [21].

The panel declared that the determination of Her-2/neu status is obligatory in all breast cancer patients. Upon occurrence of MBC, Her-2/neu status can be assessed on histological samples from metastases or the primary tumor, as changes in Her-2/neu expression/amplification have been reported to occur occasionally [9].

prognostic factors

As stated in the previous consensus [9], a number of clinical and biological prognostic factors are associated with long-term clinical outcomes among women with MBC (Table 1). Since breast cancer is a very heterogeneous disease, these criteria do not lend themselves to dichotomize risk strata, but are clinically relevant for the choice of treatment and determining prognosis.

Table 1. Prognostic factors in patients with metastatic breast cancer

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Favorable</th>
<th>Unfavorable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Performance status</td>
<td>Good</td>
<td>Poor</td>
</tr>
<tr>
<td>Sites of disease</td>
<td>Bone, soft tissue</td>
<td>Viscera, CNS</td>
</tr>
<tr>
<td>No. of sites of disease</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td>Positive</td>
<td>Positive (significance less clear in Her-2/neu inhibitors era)</td>
</tr>
<tr>
<td>Her-2/neu status</td>
<td>Negative</td>
<td></td>
</tr>
<tr>
<td>Disease-free interval</td>
<td>&gt;2 years</td>
<td>&lt;2 years</td>
</tr>
<tr>
<td>Prior adjuvant therapy</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Prior therapy for MBC</td>
<td>No</td>
<td>Yes</td>
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CNS, central nervous system; MBC, metastatic breast cancer.

endocrine treatment

In general and as recommended previously [9], endocrine treatment should be offered as first option to most women with hormone-sensitive MBC. This recommendation is based upon lower toxicity of endocrine treatment and generally longer durations of response in this subset as compared with cytotoxic chemotherapy, with no difference in OS [22]. Patients with hormone-sensitive MBC are typically characterized by

- a long disease-free interval (>2 years),
- no (or limited) visceral involvement,
- limited metastatic sites and disease-related symptoms and
- slow disease progression

Patients relapsing during or within 12 months after the end of adjuvant endocrine treatment are considered resistant to the specific endocrine drug and should be offered alternative therapies. Based upon data from early breast cancer and MBC, the concurrent use of endocrine treatment and cytotoxic chemotherapy in MBC is discouraged [9]. In patients with very limited metastatic disease, local treatments (e.g. surgical resection and radiation therapy) or watchful waiting may be considered, although there are no data from randomized trials supporting or discouraging this practice.

Only a limited amount of new important data has been generated in recent years, which would lead to a change in recommendations reached by the panel previously [9].

Briefly, the following recommendations have been reconfirmed for the endocrine treatment of postmenopausal patients with hormone receptor-positive MBC:

- The use of a third-generation nonsteroidal (anastrozole and letrozole) or steroidal (exemestane) aromatase inhibitor was recommended as first-line treatment with tamoxifen remaining to constitute a valuable option.
- Following tamoxifen failure, a third-generation aromatase inhibitor or the selective ER downregulator fulvestrant is recommended for second-line treatment.
- Following failure of a third-generation nonsteroidal aromatase inhibitor, a steroidal aromatase inhibitor [23–25], tamoxifen (or toremifen) [26], fulvestrant, progesterins, estrogen or androgens may be considered [27, 28]. In the Evaluation of Faslodex versus Exemestane Clinical Trial trial, which enrolled patients after treatment failure on nonsteroidal aromatase inhibitors, RR, PFS and OS were similar with exemestane and fulvestrant [29]. However, no definitive recommendation for a treatment cascade can be given at present.
- The different side-effect and toxicity profiles as well as the route of administration of tamoxifen, aromatase inhibitors and fulvestrant should be considered in the choice of endocrine treatment in the individual patient.

In premenopausal patients with endocrine-dependent MBC, tamoxifen, ovarian function suppression or a combination of
both continue to constitute suitable treatment options [30–32], although the combination of luteinizing hormone–releasing hormone (LH–RH) agonist and tamoxifen may be superior to LH–RH agonist alone [33]. In this population of patients, there are insufficient data on the use of aromatase inhibitors, which should be given only in conjunction with some form of adequate suppression of ovarian function [34].

cytotoxic chemotherapy

general recommendations

Chemotherapy remains the mainstay of treatment in MBC. The goals of chemotherapy in this setting are to prolong survival, alleviate or prevent tumor-related symptoms and improve QoL. However, in contrast to endocrine therapy, chemotherapy is more likely associated with considerable and notorious side-effects that have to be balanced against potential benefits. Therefore, primary chemotherapy should generally be offered to patients whose tumors are not sensitive or are refractory to hormone therapy. The candidates to chemotherapy are also patients with bulky visceral disease, severe tumor-related symptoms or rapid progression, irrespective of hormone-receptor status. At the onset of chemotherapy, an assessment of cancer-related symptoms and performance status should be carried out. Initial disease staging should allow fair assessment of the baseline tumor burden. During therapy, patient symptoms and performance status have to be recorded with each cycle. To avoid continuing ineffective therapy, tumor response should be assessed every two or three cycles. Laboratory tests should be carried out before each chemotherapy administration to secure treatment safety. Integrated assessment of chemotherapy benefits should include anticancer efficacy, amelioration of cancer-related symptoms and treatment-related side-effects. The current line of chemotherapy should be stopped if prohibitive toxicity or overt progression arises. At progression, in most instances further treatment with new agents should be considered.

There is a paucity of data on prospectively evaluated molecular predictors that could govern the individualized choice of chemotherapeutic agents in patients with MBC [35, 36]. This shortcoming, however, is expected to resolve upon successful validation of genomic information on predictors of drug sensitivity and resistance in ongoing prospective clinical trials [37].

When considering chemotherapy in MBC, the following scenarios have to be considered:

• First-line treatment
• Chemotherapy after anthracycline pretreatment
• Chemotherapy after anthracycline and taxane pretreatment

first-line treatment

sequential single-agent versus multidrug chemotherapy. An overview of randomized trials indicates that first-line multidrug chemotherapy in MBC is associated with higher RRs, longer PFS and a modest, if any, improvement in OS compared with sequential single-agent treatment administered at the maximum tolerated dose [38]. However, the randomized trials that compared combination chemotherapy with specified, sequential single-agent treatment, while confirming higher RRs, did not show improved survival [39–41]. Multidrug approach has been usually associated with increased toxicity. In contrast, a recently presented CECOG study has shown that sequential use of docetaxel and gemcitabine could result in unexpectedly higher toxicity as compared with their combined application, probably due to higher chemotherapy dosages used in the former [41]. Nevertheless, an additional benefit of single-agent sequential chemotherapy is that this strategy allows efficacy assessment of particular agents.

anthracyclines. Anthracyclines constitute the group of most active cytotoxic agents in MBC. Anthracycline-naive patients with MBC are typically applied single-agent anthracycline treatment, be it doxorubicin (60–75 mg/m² every 3 weeks or 20 mg/m² weekly) or epirubicin (75–100 mg/m² every 3 weeks or 20–30 mg/m² weekly) or anthracycline-based combinations. Patients relapsing >12 months after anthracycline-based treatment may be reinduced with anthracycline-based chemotherapy up to cumulative doxorubicin and epirubicin dose levels of 450–550 and 800–1000 mg/m², respectively. More recently, liposomal doxorubicin formulations (pegylated or not pegylated) have shown antitumor efficacy similar to that observed with nonliposomal formulations in first-line treatment of MBC, but with a low cardiac toxicity profile [40–44]. Thus, liposomal doxorubicin may be considered in patients with preexisting cardiac disease or in those who have reached or near the cumulative cardiotoxicity threshold.

taxanes. Taxanes—paclitaxel, docetaxel and nanoparticle albumin-bound paclitaxel (nab-paclitaxel)—have demonstrated significant activity in MBC in terms of RR and PFS. Several trials have explored the value of combining anthracyclines and taxanes, given that these two classes of agents have different mechanisms of action and no cross-resistance [45–50]. Most of these studies showed that combined use of anthracyclines and taxanes increased RR and time to progression (TTP), and two studies also demonstrated improved OS [46, 47], however, at the expense of higher treatment-related toxicity. A recent meta-analysis showed increased RR and PFS, but not OS of taxanes in combination with anthracyclines, compared with standard nontaxane regimens [51]. Additionally, this meta-analysis failed to identify a subset of patients who might derive clear benefit from the addition of taxanes.

other agents. Increased use of anthracyclines and taxanes as adjuvant and neoadjuvant treatments has restricted their use in patients with relapse. Several new drugs including antimetabolites (gemcitabine and capcitabine), vinca alkaloids (vinorelbine) and epothilones (ixabepilone) have shown activity in MBC. However, these compounds have typically been used in salvage chemotherapy settings; therefore, their role in first-line treatment is not well recognized.
Single-agent capecitabine was associated with RRs of ~25% [52, 53] and in the first-line treatment of MBC has provided significantly longer OS than the classical cyclophosphamide–fluorouracil–methotrexate regimen [54]. The Food and Drug Administration-approved capecitabine dose is 2500 mg/m² on days 1–14 of a 21-day cycle; however, in clinical practice, a dose of 2000 mg/m² is commonly applied, particularly in elderly patients [53].

The efficacy of first-line vinorelbine seems to be modest [55], but a combination of vinorelbine and capecitabine in an elderly population provided an RR of 43% [56]. Similarly, gemcitabine as single agent showed limited efficacy in first-line treatment of MBC. In a randomized study including elderly patients, this compound was found to be less effective than single-agent epirubicin (RR 16% versus 40%, TTP 3.4 versus 6.1 months and OS 11.8 versus 19.1 months, respectively) [57].

Accumulating data demonstrate that ‘triple-negative’ or ‘basal’ phenotype of breast cancer may represent a biologically distinct entity, and preliminary results indicate its high sensitivity to agents that bring about DNA interstrand cross-links, such as mitomycin C or platinum salts [58]. A randomized study comparing docetaxel to carboplatin in this subset of patients is currently ongoing among many other studies in clinical research.

**recommendation.** No optimal first-line chemotherapy regimen can be defined in MBC, although anthracycline-based combinations remain the most commonly used treatment regimens. In patients who have received anthracyclines in the adjuvant or neoadjuvant setting, two main treatment options include reintroduction of anthracyclines considering their cumulative dose or application of taxanes. Patients with early relapse after previous adjuvant anthracycline and taxane chemotherapy may be offered other regimens.

**chemotherapy after anthracycline pretreatment**

**taxane monotherapy.** The taxanes, applied as monotherapy or in combination with other agents, are the most commonly used compounds in MBC patients previously exposed to anthracyclines. A Cochrane analysis demonstrated a modest survival advantage of taxane-based versus nontaxane regimens in this setting [59]. Paclitaxel has been traditionally used in doses ranging from 135 to 225 mg/m² administered every 3 weeks; however, its weekly administration (usually at a dose of 80 mg/m²) provides superior RR, TTP and OS [21]. In contrast to paclitaxel, the efficacy of docetaxel does not appear to be schedule dependent [60, 61].

A direct comparison of docetaxel (100 mg/m²) and paclitaxel (175 mg/m²), both administered every 21 days, demonstrated longer TTP and OS of the former, albeit at the cost of a significantly increased toxicity [62]. Another phase III trial showed higher RR and TTP of nab-paclitaxel compared with paclitaxel (175 mg/m² over 3 h every 21 days) [63]. Administration of nab-paclitaxel was associated with a lower risk of hypersensitivity reactions, less grade 4 neutropenia, but increased grade 3 sensory neuropathy. Most recently, a phase II randomized study showed longer PFS of nab-paclitaxel (used at three different dosage levels: 300 mg/m² every 3 weeks, 100 or 150 mg/m² on days 1, 8 and 15 every 4 weeks), compared with docetaxel at 100 mg/m² every 3 weeks [64]. It should be noted, however, that neither docetaxel nor nab-paclitaxel has demonstrated superiority over the weekly schedule of paclitaxel.

**taxane-based multidrug chemotherapy.** Two randomized phase III trials including anthracycline-pretreated MBC patients demonstrated that two-drug taxane combinations (docetaxel and capecitabine, paclitaxel and gemcitabine) are associated with improved OS compared with taxane monotherapy [65, 66]. However, particularly in the case of docetaxel–capecitabine combination, multidrug therapy resulted in significantly increased hematologic and nonhematologic toxicity. Additionally, no cross-over to antimetabolites after the taxane failure was mandated in these studies, and many patients did not receive subsequent therapy. A randomized phase III trial comparing docetaxel plus gemcitabine versus docetaxel plus capecitabine showed similar efficacy of both regimens, with significantly lower nonhematologic toxicity of the former [67].

**recommendation.** In patients with anthracycline resistance or failure, taxane monotherapy (preferably docetaxel every 3 weeks, paclitaxel every week or nab-paclitaxel weekly) or taxane-based combinations should be considered, taking into account QoL, toxicity, characteristics of the disease and the ease of administration.

**chemotherapy after anthracycline and taxane pretreatment**

There are few effective treatment options available to women with MBC who failed to respond or relapsed after receiving both anthracyclines and taxanes. Several agents, including capecitabine, vinorelbine, gemcitabine, epothilones and platinum salts, as well as combinations thereof have been investigated [68]. Of those, capecitabine has been the most frequently used agent, given its efficacy, safety and ease of administration [69]. Capecitabine has also become an attractive partner for combination strategies with both cytotoxic and targeted agents [70, 71].

Gemcitabine and vinorelbine have been shown to be active in some patients pretreated with anthracyclines and taxanes [72, 73]. A randomized study demonstrated that the combination of these two agents was associated with increased PFS, but not RR and OS, compared with vinorelbine alone [72].

More recently, ixabepilone (an analogue of epothilone B), representing a new class of compounds suppressing microtubule activity, has emerged as an active agent in anthracycline and taxane-pretreated patients [74]. A recent phase III study demonstrated that addition of ixabepilone to capecitabine is associated with increased RR and PFS compared with capecitabine alone [71]. This benefit was achieved at the expense of increased toxicity, particularly sensory neuropathy and neutropenia.

**recommendation.** Based on the current experience, capecitabine, gemcitabine, liposomal doxorubicin, ixabepilone or vinorelbine, all administered as either monotherapy or in combination with other cytotoxic agents may be beneficial after
failure of anthracyclines and taxanes. Consecutive cytotoxic chemotherapy is worth considering in women who have responded to previous regimens, but no definitive guidance can be given regarding the optimal agents or the order they should be administered.

dose intensity
There are no new data demonstrating a benefit of increased chemotherapy dose intensity in MBC [75]. Thus, this strategy should not be attempted outside clinical trials.

treatment duration
Therapeutic options in MBC include continuation of chemotherapy until disease progression or treatment interruption at some point, with its reintroduction at the time of progression. A series of randomized studies compared shorter versus longer chemotherapy [76–81]. These studies have generally shown that prolonged treatment is associated with extended TTP but has little effect on OS. The impact of prolonged therapy may be drug dependent, as some agents (e.g. capecitabine) can be continued for longer periods than others (e.g. anthracyclines and taxanes). A recent systematic review of eight randomized trials including 1942 patients demonstrated an insignificant reduction in the risk of death (hazard ratio 0.92; CI 0.84–1.00; P = 0.07) with prolonged therapy [82]. Thus, the benefit associated with longer chemotherapy duration as first-line treatment in MBC seems to be at best marginal.

management of patients with Her-2/neu-overexpressing MBC
trastuzumab
Trastuzumab represents an effective single agent in HER-2/neu-overexpressing (3+ by IHC or FISH positive) MBC [83, 84]. In a pivotal, randomized phase III trial carried out in patients with HER-2/neu-overexpressing MBC, first-line treatment with the combination of trastuzumab plus chemotherapy resulted in significantly higher overall RR and significantly prolonged PFS and OS as compared with chemotherapy alone [85]. This clinical benefit was achieved with only minimal increase in the subjective toxicity profile of the combination over single-agent paclitaxel. A second randomized trial of docetaxel with or without trastuzumab has also shown benefit in OS [86]. The combination of an anthracycline and trastuzumab was also highly effective in the pivotal trial, but accompanied by a high risk of cardiotoxicity [85]. A series of other cytotoxic drugs including vinorelbine, platinum compounds, capecitabine and gemcitabine administered in patients with HER-2/neu-overexpressing MBC in combination with trastuzumab in the first and up to fifth-line setting have produced RR between 24% and 81% [87–97]. Selection of regimens is governed by the patient’s prior treatment history and the side-effect profile of concurrent therapy. Retrospective analyses and a randomized trial comparing chemotherapy and trastuzumab to trastuzumab alone followed by chemotherapy at progression demonstrated a trend favoring survival for up-front use of concurrent therapy [98, 99]. Given that, and owing to the survival advantage seen in two trials of concurrent chemotherapy and trastuzumab, the use of combination treatment is preferable to single-agent therapy for most patients.

The benefit of adding more than one cytotoxic agent over single-agent chemotherapy with trastuzumab is unclear. Addition of carboplatin to trastuzumab and paclitaxel increased RR and TTP in one randomized trial [100], whereas a similar study using docetaxel instead of paclitaxel found no benefit but reported an increased toxicity from adding the platinum salt [101]. Similarly, preliminary results from a phase II randomized trial adding capecitabine to docetaxel and trastuzumab have demonstrated benefit in terms of PFS, and not RR, the primary end point in this study [102].

Trastuzumab has also been studied in combination with endocrine therapy for ER-positive, HER-2/neu-positive MBC. In a randomized trial of anastrozole versus anastrozole and trastuzumab, the addition of trastuzumab yielded modest improvements in PFS and RR. OS, however, was found to be prolonged only in a post hoc analysis comparing patients who received trastuzumab in combination or sequential after anastrozole failure to those who did not receive trastuzumab at any time point [103, 104].

Treatment with trastuzumab may be complicated by a modestly increased risk of congestive heart failure (CHF) [105]. The risk for the development of CHF increases with advanced age and concurrent therapy with trastuzumab and anthracyclines [85]. Outside of research protocols, patients should still not receive concurrent treatment with trastuzumab and anthracyclines. However, the administration of trastuzumab in combination with less cardiotoxic anthracyclines like epirubicin or liposomal doxorubicin formulations may be relatively safe and effective [106–110]. The frequent pretreatment with anthracyclines in the adjuvant setting, the concern over cardiotoxicity and the availability of multiple nonanthracycline chemotherapy options that can be safely paired with trastuzumab make the combination of trastuzumab and anthracyclines less desirable. It was recommended that patients undergo baseline measurement of cardiac function before trastuzumab-based therapy and continue cardiac surveillance while continuing treatment. Echocardiography or radioisotope ventriculography are commonly used to assess left ventricular function before and during trastuzumab-based treatment. However, the optimal cardiac surveillance strategy remains to be established.

Patients who have achieved optimal clinical response to trastuzumab-based therapy may be considered for maintenance treatment with single-agent trastuzumab, though the clinical benefits of this practice are not known.
progressive disease during trastuzumab treatment. Ongoing use of trastuzumab beyond tumor progression as single agent or after changing the concomitant chemotherapy has been widely practiced but until recently was of unknown clinical value [113]. Retrospective studies and feasibility analyses indicate that such treatment was well tolerated by most patients [113–115].

Two randomized trials have now evaluated the role of continuing trastuzumab treatment beyond tumor progression. Von Minckwitz et al. [116] compared capecitabine alone or capecitabine plus trastuzumab among women with HER-2/neu-positive MBC progressing under previous trastuzumab-based treatment. The study demonstrated an improvement in RR and TTP, but was underpowered to demonstrate an OS benefit. Another clinical trial tested the efficacy of continuation of trastuzumab after progression of HER-2/neu-positive MBC under trastuzumab, anthracyclines and taxanes and randomized between the addition of lapatinib to trastuzumab and a switch to lapatinib only [117]. This study demonstrated a significant improvement in clinical benefit rate and TTP and a trend favoring OS among women who received a combination of lapatinib and trastuzumab.

In early-phase clinical trials, the addition of pertuzumab, an mAb targeting an epitope distinct from that bound by trastuzumab on the Her-2/neu receptor, or the Hsp90 inhibitor tanezumycin to trastuzumab have also demonstrated efficacy and safety in patients with trastuzumab-refractory MBC [118, 119]. These findings indicate that continuing trastuzumab may have clinical benefits in combination with other treatments, despite tumor progression on prior trastuzumab treatment. However, the evidence regarding the magnitude of such benefit is unknown. Similarly, in a phase II clinical trial the antibody–drug conjugate trastuzumab–DM1 exhibited single-agent activity in patients progressing under prior Her-2/neu-targeted therapy [120].

lapatinib
Several TKIs are being investigated in phase II trials in MBC. Lapatinib, an orally available TKI directed against both the erbB1 and the erbB2 (HER-2/neu) receptor, has activity in trastuzumab-resistant, HER-2/neu-positive MBC [121–123]. As a single agent, lapatinib has shown RR between 5% [124] among chemotherapy- and trastuzumab-refractory breast cancer and 24% among trastuzumab-naive patients [125]. In a pivotal trial in women with trastuzumab-resistant HER-2/neu-positive MBC, the combination of capecitabine and lapatinib was found to be significantly better than capecitabine alone in terms of disease-free survival [70]. However, OS was not significantly prolonged by the combined treatment with extended follow-up [126].

In a recently published trial, evaluating the benefit of adding lapatinib to first-line therapy with paclitaxel in patients with unknown or negative Her-2/neu status, most clinical outcomes, but not OS, were improved by addition of lapatinib to paclitaxel only in the small subgroup of Her-2/neu-positive patients [19]. When combined with letrozole in patients with hormone-dependent MBC, lapatinib is active only in the Her-2/neu-positive subgroup [127].

Patients with HER-2/neu-positive MBC have an increased risk of developing brain metastases, likely owing to several factors—a predilection for visceral sites of metastasis, a relative sanctuary site in the CNS and prolonged OS owing to the success of trastuzumab-based treatment [12]. Lapatinib has shown hints of CNS activity (although modest in heavily pretreated patients) as a single agent or in combination with capecitabine [128]. Further, in the pivotal trial of capecitabine with or without lapatinib, prevention or delay in the development of CNS metastases with lapatinib was indicated [126]. Nevertheless, treatment of CNS metastases remains a clinical challenge. At present, there are no data on prophylactic therapy or on the long-term clinical benefit of surveillance in asymptomatic patients.

antiangiogenic treatment
bevacizumab
Bevacizumab is a humanized mAb directed against the vascular endothelial growth factor (VEGF) and is the most mature therapeutic agent specifically designed to disrupt angiogenesis. Common side-effects include hypertension, nasal congestion/discharge and slight exacerbation of chemotherapy-related side-effects [129].

Three phase III trials have evaluated the efficacy of chemotherapy alone or chemotherapy plus bevacizumab for MBC. The first published study compared capecitabine alone or capecitabine plus bevacizumab in patients with extensive chemotherapy exposure including anthracyclines and taxanes [130]. Although RRs increased substantially in the bevacizumab arm, there was no prolonged PFS or OS. In contrast, a second trial, ECOG2100, comparing weekly paclitaxel with or without bevacizumab as first-line therapy for MBC, demonstrated a significant improvement in RR and time to disease...
progression with bevacizumab (5.5 versus 11.6 months) [131]. The third study [132], comparing docetaxel with or without bevacizumab as first-line treatment, again demonstrated improvement in TTP, though of far less absolute difference than seen in ECOG2100. To date, none of the trials of bevacizumab has shown a survival advantage. Thus, in first-line treatment, bevacizumab in combination with taxanes appears to improve upon results seen with chemotherapy alone, making combination treatment an option for such patients. In contrast, there are no data indicating a benefit of bevacizumab use in the second-line chemotherapy.

bisphosphonates

bisphosphonate therapy for bone metastases
clodronate (oral). Several small placebo-controlled trials have examined the efficacy of oral clodronate in patients with bone metastases from breast cancer [133–135]. Overall, patients who received oral clodronate had a significantly reduced skeletal morbidity rate compared with patients who received placebo.

ibandronate (oral and i.v.). The efficacy of oral and i.v. ibandronate has been evaluated in randomized, placebo-controlled trials in women with bone metastases from breast cancer [136]. Two years of i.v. ibandronate therapy significantly reduced the mean skeletal morbidity period rate and lengthened the median time to first bone event compared with placebo. A pooled analysis of two phase III studies of oral ibandronate showed a significant reduction in the risk of bone events compared with placebo [137].

zoledronic acid (i.v.). Intravenous zoledronic acid has been shown to be superior to pamidronate in treatment of hypercalcemia of malignancy (HCM) [138] and in reducing the risk of skeletal-related events (SREs) in large randomized trials in breast cancer patients with bone metastases [139, 140]. Overall, patients with MBC receiving zoledronic acid experienced a higher reduction in the risk of developing an SRE compared with patients receiving pamidronate [139]. Zoledronic acid also significantly prolonged the mean time to first SRE and significantly reduced the annual skeletal morbidity rate compared with pamidronate [139–141]. A subsequent study compared zoledronic acid with placebo in patients with breast cancer and bone metastases. In this trial, patients who received zoledronic acid had a significantly longer median time to first SRE and a significantly reduced risk of experiencing an SRE compared with placebo [142].

pamidronate (i.v.). The efficacy of i.v. pamidronate for the prevention of SREs has been demonstrated in two large randomized phase III trials in patients with at least one osteolytic bone lesion [143, 144]. In both trials, pamidronate significantly lowered bone pain scores at the end of treatment compared with placebo. A pooled analysis of these two trials showed that pamidronate significantly increased the time to first SRE, significantly reduced the proportion of patients who experienced SREs and significantly reduced the skeletal morbidity rate compared with placebo [145].

recommendations. The strongest evidence for efficacy in prevention of skeletal morbidity in patients with breast cancer and bone metastases is available for i.v. bisphosphonate preparations, but no trial has directly compared oral with i.v. preparations. Evidence from randomized clinical trials in patients with breast cancer and bone metastases indicates that the use of bisphosphonates (oral clodronate 1600 mg/day, i.v. ibandronate 6 mg every 21–28 days, oral ibandronate 50 mg/day, i.v. pamidronate 90 mg every 21–28 days and i.v. zoledronic acid 4 mg every 21–28 days) can reduce and delay the incidence of skeletal morbidity [146]. Evidence supports the use of bisphosphonates with or without other anticancer treatment. Although most trials evaluated bisphosphonate treatment administered for a maximum of 2 years, the optimal duration of this treatment is unknown. The American Society of Clinical Oncology guidelines on the use of bisphosphonates in women with breast cancer recommend that bisphosphonate therapy should be continued until there is a substantial decline in patient performance status [147]. Currently, there are insufficient data on the use of bisphosphonates in women without metastatic bone involvement or without HCM.

safety considerations during bisphosphonate therapy

Overall, bisphosphonate therapy is generally well tolerated in patients with advanced breast cancer metastatic to bone and can be safely combined with other anticancer therapies. Oral bisphosphonates are associated with gastrointestinal side-effects [148] and i.v. bisphosphonates are associated with transient influenza-like symptoms and increased bone pain after the initial infusions [148]. In addition, dose- and infusion rate-dependent effects of bisphosphonates on renal function have been reported [148]. Guidelines have been published which recommend monitoring renal function in patients receiving bisphosphonates and alternative dosing schedules for patients with renal impairment [149]. Recently, an uncommon toxicity consisting of osteonecrosis of the jaw (ONJ) has been reported in patients accompanying prolonged use of bisphosphonates [150]. Risk factors for ONJ may include poor oral hygiene and dental surgery during bisphosphonate therapy. Therefore, preventive dentistry recommendations have been published [150–152]. Preliminary reports indicate that implementation of preventative dentistry and monitoring recommendations can substantially reduce the incidence of ONJ in patients with cancer [153].

supportive care

symptomatic anemia

As mentioned previously [9], anemia constitutes a common problem in patients with metastatic disease and may be caused or aggravated by cytotoxic treatment resulting in fatigue. When present, also other reasons for fatigue and associated symptoms including nutritional status, treatment side-effects and psychological and psychiatric disorders should be considered and comprehensively investigated.

Symptomatic anemia (with a hemoglobin <10–11 g/dl) should be diagnosed, investigated and corrected to maintain
QoL and avoid fatigue [154]. Under consideration of various geographic approaches, erythropoiesis-stimulating proteins (ESPs) and erythrocyte transfusions constitute reasonable options to achieve this goal. However, the use of some ESPs has shortened OS and/or increased the risk of serious thrombovascular events or tumor progression/recurrence in some clinical studies in patients with breast, non-small-cell lung, head and neck, lymphoid and cervical cancers [155, 156]. To decrease these risks, it is recommended, therefore, to use the lowest dose of ESP needed to avoid red blood cell transfusions and use ESPs only for treatment of symptomatic anemia associated with concomitant myelosuppressive chemotherapy. The treatment should be discontinued when a hemoglobin level of 11–12 g/dl has been reached. With adequate dosing and schedule, there is no evidence of superiority of any ESP [157–159]. In the case of nonresponsiveness to ESPs and for acute symptoms, erythrocyte transfusions should be administered.

leukopenia
When using chemotherapy associated with a likelihood of >20% of febrile leukopenia, a history of previous febrile neutropenia under preceding chemotherapy or due to individual risk factors, the use of myeloid colony-stimulating factors can be considered [160–163].

psychological support
As recognized before [9], women with MBC may experience psychological distress including depression, anxiety, stress–response syndrome, difficulty in coping and social isolation. Randomized trials of group psychosocial interventions in patients with MBC identified psychological benefits specifically including improvement in mood, pain control and coping. Therefore, it was recommended that psychosocial support should be available to patients with MBC. However, current research does not allow for the recommendation of an optimal type, timing or duration of psychological support interventions. Moreover, the evidence of a survival advantage due to psychological support interventions is not convincing.

menopausal symptoms, hormone replacement therapy and topical estrogen
Menopausal symptoms crucially impair women’s QoL and are frequently aggravated by endocrine therapy or cytotoxic therapy in women with breast cancer. Based upon scientific evidence causally linking the use of HRT to the development of breast cancer [164, 165], the use of HRT in MBC is strongly discouraged, as HRT may stimulate growth of hormone receptor-positive cancers. In this vein, several reports about a clinical benefit of HRT withdrawal in MBC have been published [166, 167]. Likewise, in the absence of safety data on the use of HRT in patients with ER- and PgR-negative tumors, the panel strongly discouraged the use of HRT in all patients with MBC. If topical estrogens need to be considered for QoL reasons, preparations that result in the lowest possible systemic absorption should be chosen. Vaginal estradiol tablets should be used with caution in MBC patients, whereas estradiol suppositories may be less dangerous [168]. Whenever feasible, nonhormonal treatment of menopausal symptoms should be sought, which may include pharmacological interventions, mind–body and behavioral interventions [169–173].

surgical resection of the primary tumor in metastatic disease
The benefit of surgical resection of the primary tumor in patients presenting with metastatic (stage IV) breast cancer is not established. However, recent retrospective reviews of patient records have indicated that such intervention might improve clinical outcomes. In two separate chart reviews involving >800 patients, median OS was increased by 10–16 months in patients who underwent surgical resection (P < 0.0001 compared with patients who did not undergo surgery) [174, 175]. However, another chart review of 147 patients found the benefit of surgery only in patients who underwent surgery before the diagnosis of metastatic disease [176]. Surgical removal of the primary tumor has been identified as an independent predictor of improved outcome (OS or PFS) in multivariate analyses among patients with stage IV disease and intact primary tumors [177, 178]. It should, however, be noted that these findings have not been validated to date in prospective studies, and the real benefits of surgery in patients with MBC remain to be elucidated.

emerging treatments and future directions
A rapidly increasing number of molecular structures of malignant cells can be targeted by various agents including signal transduction inhibitors, mAbs, anticancer vaccines, antisense strategies or antiangiogenic drugs. Because the mode of action of the various available agents is distinct from cytotoxic treatment, they represent ideal combination partners for chemotherapeutic and endocrine treatment options. These emerging approaches, however, will require additional efforts for careful selection of patients most likely to benefit from targeted therapies: Proper definition of targets and assessment of target inhibition in tumors or indicative tissues, determination of the mechanisms of drug sensitivity and resistance and assessment of novel surrogate end points of treatment effect may require assessment of an increasing number of biological traits of patients and tumors alike, functional imaging, repeated biopsies and storage of biological material suitable for molecular and high-throughput analyses.

emerging treatments
antiangiogenic therapy. Following the encouraging results from the use of bevacizumab in the first-line treatment of MBC, results from additional randomized trials combining bevacizumab with other targeted therapies [179] are eagerly expected. In addition, there are numerous trials of other anti-VEGF agents alone or in combination ongoing for advanced breast cancer [180, 181]. As yet, no other drugs apart from bevacizumab based upon the concept of antiangiogenesis are approved for use. Another investigated strategy includes continuous administration of low-dose cytotoxic drugs (metronomic chemotherapy). This nontoxic and easily
deliverable scheduling is believed to induce anticancer effect at least in part by virtue of antiangiogenic mechanisms. Two trials using low-dose cyclophosphamide (50 mg daily) and methotrexate (5 mg daily twice a week) have shown a RR in the range of 20% [182, 183]. Metronomic therapy may be potentially useful in pretreated or frail MBC patients, but it still warrants clinical verification.

cetuximab. The monoclonal epidermal growth factor receptor (EGFR) antibody cetuximab has shown little activity as single agent in patients with mostly heavily pretreated MBC in randomized phase II studies, but may add to the efficacy of cytotoxic treatment [184, 185]. Inhibition of the EGFR is presently investigated as a new treatment strategy specifically in patients with triple-negative breast cancer.

**future directions**

targeting DNA repair mechanisms. A significant fraction of breast cancer is hereditary and based on germline mutations in the breast cancer early onset (BRCA) genes BRCA1 and BRCA2. In addition, both genes are found inactivated in sporadic cases by mutations and more often by epigenetic mechanisms. Both BRCA1 and BRCA2 are at least partially necessary for DNA repair by homologous recombination (HR). HR gets additional importance in cells if another classical DNA recombination pathway, namely the repair of single-stranded DNA (SSDNA) is blocked. In normal cells, the inhibition of a crucial enzyme of SSDNA repair, poly ADP-ribose polymerase (PARP1), does not cause major effects. When SSDNA breaks are encountered during DNA replication, the replication fork stalls and double-stranded DNA (dsDNA) breaks accumulate. These dsDNA breaks are then repaired via HR repair, an error-free repair mechanism. In contrast, tumors lacking BRCA may be highly sensitive to PARP1 inhibitors [186]. Thus, PARP1 inhibitors alone or in combination may prove highly effective therapies for cancers with lacking BRCA due to their high sensitivity to the inhibitor and the lack of deleterious effects of these compounds on the remaining healthy cells with functioning BRCA HR pathway [187].

anticancer vaccines. The field of cancer vaccines is currently in active preclinical and clinical investigations. Although no therapeutic breast cancer vaccine has been approved to date, recent preclinical and clinical findings have shown that the use of vaccine therapies may well lead to an additional treatment choice, ultimately being used for the therapy of advanced breast cancer.

One of the two structures mainly used as targets for an active immune response, HER-2/neu, emerged from the dramatic response to this receptor by passive immune therapy by trastuzumab or pertuzumab [188]. The second commonly used target structure Mucin 1 (MUC1), a transmembrane glycoprotein was used in several vaccination trials [189]. All these trials with varying vaccination strategies (i.e. peptide based, dendritic cell based and others), with different adjuvants, showed very limited toxic effects and consistent immunological responses of the patients, but in general low or absent clinical responses in patients with MBC. Patients with limited or minimal tumor burden, however, may be a better target population for therapeutic vaccine therapies.

proteomics as a tool to define biomarkers. Biomarkers serve as hallmarks for the status of tumor growth at a given time and change during the disease process. In general, biomarkers can guide us to define subgroups of patients whose tumors express a specific target and thus may have a high probability of response. Therefore, the identification of novel biomarkers that are able to predict treatment response or resistance may allow therapy to be tailored to individual patients. Cancer proteomics is a rapidly developing field and is expected to accelerate the discovery of new diagnostic, prognostic and therapy-related biomarkers. The rationale for proteomic investigation is that proteins are often expressed in quantities and physical forms that cannot be predicted from DNA and messenger RNA analysis, as for example due to post-translational modification of proteins. Therefore, proteome analysis provides a complementary approach to microarray gene expression profiling [37, 190].

Application of protein microarray technology for the study of ongoing signaling activity within breast tumor specimens holds great potential for elucidating and profiling signaling activity for patient-tailored therapy. Analysis of laser capture microdissected primary human breast tumors and metastatic lesions reveals pathway specific profiles and a new way to classify cancer based on functional signaling portraits. Moreover, the metastasis-specific changes that occur within a new microenvironment can be revealed. Analysis of biopsy material from clinical trials for targeted therapeutics demonstrates the feasibility and utility of comprehensive signal pathway activation profiling for molecular analysis [191, 192]. The possibility of detecting hundreds to thousands of proteins at the same point of time is also a tool to define proteins associated with response or resistance to therapy [193].

**funding**

Bristol Myers-Squibb; Eli Lilly; Roche.

**acknowledgements**

The panelists thank Ursula Fischer for the organization of the infrastructure of this consensus. Pamela Goodwin (Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada) is a contributor to this work.

Organizing institution: CECOG, Headoffice: Schlagergasse 6, Vienna, Austria (www.cecog.org).

Supporting institution: Clinical Division of Oncology, Department of Medicine I/Cancer Center, General Hospital, Medical University Vienna, Vienna, Austria (www.meduniwien.ac.at/krebszentrum).

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