Second consensus on medical treatment of metastatic breast cancer


Central European Cooperative Oncology Group (CECOG)§, Schwarzspanierstrasse 7/5, A-1090 Vienna, Austria

Received 20 February 2006; revised 26 May 2006; accepted 26 May 2006

The present consensus manuscript defines evidence-based recommendations for state-of-the-art treatment of metastatic breast cancer depending on disease-associated and biologic variables.

Key words: chemotherapy, endocrine therapy, medical treatment, metastatic breast cancer, targeted therapy

introduction

Breast cancer is the most common malignancy among women in the Western hemisphere. Whereas a series of consensus statements have established neoadjuvant and adjuvant treatment as well as surgery as state-of-the-art treatment in patients with early breast cancer, only marginal understanding has been reached concerning an internationally accepted consensus on therapy of metastatic or advanced breast cancer (MBC).

The primary goals of treatment in MBC may include:
- Maximizing the quality of life
- Prevention and palliation of symptoms
- Prolongation of survival

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 the metastases,
- HER-2/neu status,
- the duration (<2 years versus >2 years) of the relapse-free interval since primary diagnosis of breast cancer,
- the location of metastases (visceral versus non-visceral),
- previous treatment and its effects and tolerance
- patient symptoms,
- patient preferences,
- anticipated side effects of treatment,
- the availability and access to treatment.

Treatment choices for MBC include endocrine treatment, cytotoxic chemotherapy, non-endocrine ‘targeted therapy’, bisphosphonates, and supportive measures. In individual cases local treatment modalities should also be taken into consideration.

The present consensus conference was initiated in order to define evidence-based recommendations for state-of-the-art treatment of MBC depending on the previously mentioned disease-associated and biologic variables. This document represents an update of a previous consensus reached and published in 2003 [1].

methods of consensus formation

panel composition

The Central European Cooperative Oncology Group (CECOG) convened an Expert Panel consisting of experts in clinical medicine (i.e. medical and surgical oncology) and clinical and translational research with a focus on expertise in breast cancer. The Panel participants are representatives from Australia, Canada, Europe and The United States of America and are listed at the end of this manuscript.

literature review and analysis

Metastatic breast cancer was defined according to the TNM system classification (6th edition) of the American Joint Committee on Cancer (AJCC) as any T any N, M1 tumor of the breast [2]. Randomized clinical trials on the treatment of patients with MBC have frequently also included patients with ipsilateral supraclavicular nodes as the only site of active disease. According to current knowledge, these patients should receive both, systemic and local therapy with curative intent. Thus, the present recommendations of the consensus panel are suitable for patients with stage IV disease.

Electronic and manual searches including Medline and The Cochrane Library (search terms: breast cancer, metastatic, clinical trial) and abstracts published in the proceedings of meetings of the American Society of Clinical
method of consensus formation

The Panel was divided into subcommittees of two to six participants each. Each subcommittee was assigned a coordinator and independently reviewed publications addressing particular aspects relating to the medical management of metastatic breast cancer including: (a) Diagnostics, (b) Prognostic factors, (c) Endocrine treatment, (d) Cytotoxic therapy, (e) Choice of chemotherapy or endocrine therapy, (f) Trastuzumab-based treatment, (g) Bisphosphonates, (h) Supportive care, and (i) Future directions.

Each subcommittee independently reviewed and summarized the data available until May 2005 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 at the consensus meeting. Recommendations of the consensus meeting panel represent statements that all participants of the meeting panel agreed upon.

All members of the Panel participated in the preparation of the draft guideline document, which was then repeatedly disseminated for review by the entire panel. Final text editing was completed by Christoph C. Zielinski and Wolfgang J. Kostler and accepted by all panelists.

diagnosis of metastatic breast cancer and assessment of biologic variables

The panel agreed that histological or cytological verification of metastatic disease is not required routinely. However, a biopsy of a metastatic lesion may be advisable in certain circumstances, particularly in the low range between 1 and 10% of positively staining cells—still need to be determined.

recommendations for the assessment of steroid receptor expression

Standardized testing and quality control of steroid receptor determination should be mandated, especially since the discordance rate between local and central laboratory testing for ER and PgR is high [4, 5]. ER and PgR expression should be reported in a quantified way. Despite the long use of IHC for decision making for endocrine therapy, standardized clinically relevant cut-off levels for steroid receptor positivity—

recommendations for the assessment of Her-2/neu protein overexpression and gene amplification

Her-2/neu status assessed by IHC or FISH is required for optimal decision making for the treatment of MBC. Chromogenic in situ hybridization (CISH) is emerging as a new promising technique which should be closely followed. The level of concordance between Her-2/neu 3+ overexpression assessed by IHC and FISH or CISH is high when performed in central laboratories with appropriate expertise [6–8]. By contrast, in tumors with 2+ protein overexpression by IHC, FISH testing should be performed for the decision on an indication for treatment with trastuzumab. Efforts to standardize testing for Her-2/neu overexpression are clearly required. It was encouraged to prepare material for Her-2/neu testing according to the manufacturer’s recommendations and to use the standardized IHC assay and scoring system (HercepTest®, DAKO Inc.). A recent publication strongly endorsed the use of FISH as the preferred method to select patients for trastuzumab therapy [9].

If Her-2/neu status has not been determined from the primary tumor or is unknown, Her-2/neu should be assessed on histologic samples from metastases or the primary tumor. Changes in Her-2/neu expression/amplification have been reported to occur only occasionally during the clinical evolution of early to metastatic breast cancer. Thus, routine reassessment of Her-2/neu status of metastatic lesions cannot be recommended.

prognostic factors

A number of clinical and biological prognostic factors are associated with long-term clinical outcomes among women with MBC. Because breast cancer is a very heterogeneous disease, these criteria do not lend themselves to dichotomize risk strata. However, these factors are clinically relevant for the choice of treatment and determining prognosis.

<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</td>
</tr>
<tr>
<td>No. of sites of disease</td>
<td>Oligo</td>
<td>Multiple</td>
</tr>
<tr>
<td>Hormone receptor status</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Her-2/neu status</td>
<td>Negative</td>
<td>Positive (significance less clear in trastuzumab era)</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>
</tr>
</tbody>
</table>
The panelists acknowledged that this classification should not be regarded as rigid, but may constitute the basis for treatment recommendations.

**endocrine treatment**

In general, endocrine treatment should be offered as first option to most women with hormone sensitive MBC. This subset of patients is typically characterized by:

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

Patients relapsing during adjuvant endocrine treatment are considered resistant to the specific endocrine drug and should be offered alternative therapies. Patients relapsing after adjuvant endocrine treatment may remain sensitive to primary endocrine therapy.

**endocrine treatment for postmenopausal patients**

The selective estrogen receptor modulator tamoxifen has been considered as first-line treatment for postmenopausal women with hormone-sensitive MBC for more than 20 years. The nonspecific aromatase inhibitor aminoglutethimide and the progestins medroxyprogesterone acetate and megestrol acetate were candidates for second-line therapy. These endocrine therapies were not superior to tamoxifen when used for first-line treatment. Combined endocrine therapies offered no benefit compared with single-agent tamoxifen. Treatment options recently increased with fulvestrant and third-generation aromatase inhibitors (AI). The latter were found to be superior to progestins or aminoglutethimide in second line treatment of endocrine sensitive MBC after tamoxifen failure, mainly due to improved toxicity profiles.

The third generation aromatase inhibitors include two families of drugs, nonsteroidal (anastrozole and letrozole) and steroidal inhibitors (exemestane). Fulvestrant, a selective estrogen receptor downregulator, is a novel endocrine agent which binds to ER with similar affinity as estradiol and produces a loss of ER within the tumor. Tamoxifen, AI’s and fulvestrant have different side-effect and toxicity profiles, which must be considered in the choice of endocrine treatment in the individual patient.

**first line endocrine therapy**

**aromatase inhibitors versus tamoxifen**

**anastrozole versus tamoxifen.** Two randomized phase III trials compared anastrozole with tamoxifen. Out of those, one study showed longer time to progression for anastrozole, whereas the other did not find a difference for any analysed endpoint. The overall conclusion from these studies is that anastrozole was at least as effective as tamoxifen [10–13].

**letrozole versus tamoxifen.** A randomized phase III trial compared letrozole to tamoxifen. Patients receiving letrozole had significantly longer time to progression (TTP) and overall response rate (ORR) as compared to those receiving tamoxifen. These two endpoints favored letrozole in all subgroups according to dominant site of metastatic disease, receptor status or prior adjuvant endocrine treatment. There was no significant overall survival (OS) difference though between letrozole and tamoxifen [14, 15].

**exemestane versus tamoxifen.** In a randomized phase III trial exemestane was superior to tamoxifen in terms of ORR and TTP [16]. Data on OS are not yet available.

**fulvestrant versus tamoxifen.** A randomized phase III study showed no difference between fulvestrant and tamoxifen in terms of ORR and TTP, however OS favored tamoxifen [17].

**recommendation**

Based upon the more favorable toxicity profile, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) is recommended as first-line treatment for postmenopausal patients with hormone receptor-positive MBC, but tamoxifen remains a valuable option.

**second line endocrine therapy**

Following failure of tamoxifen, the following studies have been performed:

**third generation aromatase inhibitors versus progestins or aminoglutethimide.** A series of randomized phase III studies showed the superiority of 3rd generation aromatase inhibitors versus the previously used progestins or aminoglutethimide [18–22].

**anastrozole versus letrozole.** A phase III study found no difference in TTP and OS in the intent to treat analysis and ORR favored letrozol. There was no difference for any endpoint though in the relevant ER-positive patient population [23].

**anastrozole versus fulvestrant.** Two randomized phase III studies showed no significant difference in terms of ORR and TTP [24–26].

**recommendation**

Following tamoxifen failure, the use of a third generation aromatase inhibitor (anastrozole, letrozole, exemestane) or fulvestrant are recommended for second-line treatment for postmenopausal patients with hormone receptor-positive MBC based upon the more favorable side-effect profile.

**treatment cascade after failure of aromatase inhibitors**

In the case of failure of third generation aromatase inhibitors, a steroidal aromatase inhibitor after failure of non-steroidal compounds [27–29], tamoxifen (or toremifene) [30], fulvestrant, progestins, high dose estrogens or androgens may be considered. However, no definitive recommendation for a treatment cascade can be given at present.

**endocrine treatment for premenopausal patients**

Tamoxifen, ovarian function suppression, or a combination of both are suitable options for endocrine treatment of premenopausal patients. Three small randomized studies have compared the combination of tamoxifen and LHRH agonist versus LHRH agonist alone [31–33]. A small meta-analysis
combined these data and suggested that combination of LH-RH agonist and tamoxifen may be superior to LH-RH agonist alone in all analyzed efficacy parameters (OS, PFS, RR) [34]. At present, there are insufficient data on the use of aromatase inhibitors or fulvestrant in premenopausal patients. If aromatase inhibitors are considered, they definitely should be given in conjunction with some form of ovarian function suppression.

cytotoxic chemotherapy

**efficacy of monotherapy versus polychemotherapy**

Although definitive data from randomized clinical trials are insufficient, it was suggested that single-agent therapies with various cytotoxic agents with proven efficacy in breast cancer are a reasonable option for maximizing quality of life and limiting drug toxicity, especially in patients with ER-negative, slowly progressive MBC. An overview of randomized trials suggests that polychemotherapy gives higher response rates and longer progression-free survival and a modest improvement in overall survival compared to single-agent treatment, but at the cost of significantly increased toxicity [35]. On the other hand, the only major randomized study comparing sequential monotherapies with combined anthracyclines and taxanes did not demonstrate improved survival or quality of life with the latter approach, despite increased response rates [36].

**recommendation**

The choice between polychemotherapy and sequential single agent chemotherapy should take into account the prognosis, performance status, symptom control and toxicity profiles with the ultimate goal of optimizing quality and quantity of life.

definition of optimal first-line chemotherapy

As anthracyclines and taxanes constitute the most active cytotoxic agents in breast cancer, their use in various schedules as monotherapy and as polychemotherapy is justly widely practiced. It has to be considered, however, that common practice includes anthracyclines in adjuvant chemotherapy protocols and cumulative anthracycline dosage is associated with increased rates of cardiotoxicity. The increasing use of taxanes in adjuvant and neoadjuvant treatment will potentially alter treatment strategies of patients with MBC in the near future. Patients with MBC who have never received anthracyclines should receive anthracycline-based treatment, such as doxorubicin (60 mg/m^2 every 3 weeks), epirubicin (100 mg/m^2 every 3 weeks) or liposomal doxorubicin formulations [37–39]. Patients relapsing more than 12 months after anthracycline-based treatment may be reinduced with anthracycline-based chemotherapy up to cumulative doxorubicin and epirubicin dose levels of 450–550 mg/m^2 and 800–1000 mg/m^2, respectively. Moreover, it was stressed that particular attention should be given to the possibility of a detrimental interaction between paclitaxel and doxorubicin when given concomitantly, resulting in high incidence of treatment-associated cardiotoxicity. Based on the current data base, no definitive recommendation for optimal first-line chemotherapy for patients with MBC can be given. This is due to the fact that response rates of first-line chemotherapy rarely translate into a survival benefit and data on OS from randomized phase III trials may be confounded by treatment changes after disease progression. Data from available randomized trials have clearly shown that the combined use of anthracyclines and taxanes increased ORR and also TTP in some trials [40–46]. In addition, two randomized studies have demonstrated improved OS [40, 41]. These benefits were achieved at the cost of higher treatment-related toxicity.

**recommendation**

It was suggested that due to increased ORR and increased TTP observed in randomized trials, anthracycline- and/or taxane-based regimens are to be preferred as first-line treatment in symptomatic patients and/or those with rapidly progressive disease. In patients who have received anthracyclines and/or taxanes in the adjuvant or neoadjuvant setting this strategy may have to be modified in the future, but there are no data from randomised clinical trials addressing that issue. Reintroduction of anthracyclines and taxanes in patients relapsing more than a year after completion of adjuvant therapy or, alternatively, other regimens in patients with shorter disease-free periods may be considered.

definition of optimal first-line chemotherapy

**paclitaxel.** A number of trials have evaluated the optimal dose and schedule of paclitaxel for metastatic breast cancer as first-line treatment or salvage therapy. There is no evidence of a clear-cut dose-response relationship of paclitaxel used in the range of 135–225 mg/m^2 administered q. 21 days, yet of increased toxicity with increased dose [47, 48]. The weekly administration of paclitaxel may result in better treatment outcomes and limited hematologic toxicity, but at the expense of increased therapeutic costs and neurotoxicity as compared to three-weekly administration [49, 50].

**docetaxel.** In a phase III study, docetaxel at a dose of 100 mg/m^2 was associated with a higher response rate compared to doses of 60 mg/m^2 and 75 mg/m^2, respectively [51]. One randomized phase III trial failed to show an advantage in the primary endpoint ORR, but a significant increase in TTP and OS of docetaxel (100 mg/m^2) over paclitaxel (175 mg/m^2), both administered q. 21 days at the cost of a significantly increased hematologic and non-hematologic toxicity [52]. The optimal schedule of administration of docetaxel (weekly vs. three-weekly) is unresolved [53].

**nanoparticle albumin paclitaxel (ABI-007, Abraxane).** A phase III trial comparing weekly intravenous ABI-007 with a conventional dose and schedule of paclitaxel (175 mg/m^2 over 3 hours q. 21 days) demonstrated a significantly higher ORR and TTP for the former. Administration of ABI-007 was associated with a lower risk of hypersensitivity reaction, less grade 4 neutropenia, but increased grade 3 sensory neuropathy [54].

**polychemotherapy**

Two randomized phase III trials including anthracycline-pretreated MBC patients demonstrated improved OS with polychemotherapy compared to single-agent therapy. In one study, the combination of docetaxel plus capecitabine was
superior to single-agent docetaxel, with improved RR, TTP and OS [55]. The combination resulted in significantly increased hematologic and non-hematologic toxicity. Another randomized phase III trial compared paclitaxel plus gemcitabine with paclitaxel [56]. The combination improved ORR, TTP and OS. The gemcitabine-containing arm was also associated with greater pain relief and better quality of life. Data from these two randomized trials demonstrated that the combination of a taxane with capcitabine or gemcitabine could improve OS in patients with metastatic breast cancer. Whether the sequential use of the drugs used in those two combinations could have resulted in a similar survival advantage as the combinations was not tested. A randomized phase III trial compared docetaxel plus gemcitabine (DG) with docetaxel plus capcitabine (DC) and showed similar efficacy of DG and DC, but significantly lower non-hematologic toxicity of the former [57].

**recommen**

In patients with anthracycline-resistance or failure, considered for further chemotherapy, taxane-based treatment (monotherapy or combination of a taxane with gemcitabine or capcitabine) should be used, taking into account quality of life, toxicity, characteristics of the disease and the ease of administration.

**chemotherapy after taxanes and/or anthracyclines**

While an abundance of phase II trials have been performed in patients with MBC pretreated with various cytotoxic agents, very few randomized phase III trials have addressed optimal selection of treatment after failure of taxanes and/or anthracyclines. Considering the large number of drugs available for this indication, randomized phase III trials in this setting were strongly encouraged. Quality of life is the major consideration in patients with MBC progressing after anthracyclines and taxanes. Based upon currently available phase II trials, capcitabine, gemcitabine, liposomal doxorubicin [39] or vinorelbine, all administered as either monotherapy or in combination with other cytotoxic agents may be beneficial after failure of anthracyclines and/or taxanes. Further 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**

Randomized clinical trials clearly indicate that lowering the dose of many cytotoxic drugs used for the treatment of patients with MBC can be detrimental to treatment outcome, as compared to the administration of standard chemotherapy doses [51, 58]. It was recommended, therefore, that the planned dose of cytotoxic agents should not be deliberately decreased. However, the panelists realized that dose reductions may be necessary in a significant proportion of patients to avoid excessive toxicity lowering quality-of-life.

In contrast, moderately increased dose intensity above standard level, be it with or without the use of colony stimulating factors, has not been associated with increased survival [59–64]. Thus, increased cytotoxic drug dosage over standard levels should not be used outside of controlled clinical trials. High-dose chemotherapy with autologous stem cell support has not fulfilled its promise and should not be administered outside of clinical trials [65].

**treatment duration**

A systematic review of four published randomized trials including 766 women shows that treatment with a higher number of cycles of chemotherapy is associated with longer survival (hazard ratio 1.23) and better quality of life than the same chemotherapy given for fewer cycles [66]. A more recent EORTC randomized trial showed no benefit for continuing CMF beyond six cycles [67]. These trials used chemotherapy regimens standard in the 1990s.

There is no information about the optimal duration of taxanes, capcitabine, vinorelbine and other newer agents. However, a recent trial showed no benefit for continuing paclitaxel after first achieving a response with an anthracycline and paclitaxel [68]. These data support the following recommendations:

- optimal decision-making about whether to continue chemotherapy should be based on discussions between the patient and her doctor;
- symptoms, signs, side effects, quality of life and preferences should be monitored and taken into account;
- it is reasonable to continue chemotherapy for advanced breast cancer in the absence of disease progression or significant side effects. However, patients with stable disease or optimal treatment response may take treatment breaks without undue concern over impaired long-term outcomes.

The use of endocrine treatment in hormone receptor-positive tumors for maintenance following cytotoxic chemotherapy is common practice. There is no evidence to support or discourage this practice; however the panel considered it to be a reasonable option.

**choice of chemotherapy or endocrine therapy in MBC**

**treatment cascade**

In women with slowly progressive hormone receptor-positive MBC, a policy of first-line treatment by endocrine therapy rather than chemotherapy is recommended. This recommendation is based upon reduced toxicity of endocrine treatment, and generally longer durations of response as compared to cytotoxic chemotherapy, with no difference in OS [69].

**concurrent use of endocrine and cytotoxic chemotherapy**

Based upon data from early and metastatic breast cancer, the concurrent use of endocrine treatment and cytotoxic chemotherapy in MBC should not be encouraged.

**trastuzumab-based treatment**

Trastuzumab is an effective single agent in HER-2/neu overexpressing (3+ by IHC or FISH-positive) MBC [70, 71].
In a pivotal, randomized phase III trial performed in patients with HER-2/neu overexpressing MBC, first-line treatment with the combination of trastuzumab plus chemotherapy has been shown to result in significantly higher ORR and significantly prolonged OS as compared with chemotherapy alone [72]. 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 [73]. The combination of an anthracycline and trastuzumab was also highly effective in the pivotal trial, although complicated by a high risk of cardiotoxicity [72]. A series of other cytotoxic drugs including vinorelbine, platinum compounds, capcitabine and gemcitabine in combination with trastuzumab have been suggested to be highly active in phase II trials while triple combinations including a platinum salt, a taxane and trastuzumab also look promising [74–80]. Treatment with trastuzumab may be complicated by a modestly increased risk of congestive heart failure (CHF) [39]. The risk for the development of CHF increases with advanced age and concurrent therapy with trastuzumab and anthracyclines. Outside of research protocols, patients should still not receive concurrent treatment with trastuzumab and anthracyclines, although preliminary data of several studies suggested acceptable cardiac safety and efficacy parameters with anthracycline/trastuzumab combinations. It was recommended that patients undergo baseline measurement of cardiac function prior to trastuzumab–based therapy and continue cardiac surveillance while continuing treatment. The optimal cardiac surveillance strategy is not known.

**trastuzumab in combination with cytotoxic chemotherapy**

In phase II trials, combinations of trastuzumab, with paclitaxel, docetaxel, cisplatin, carboplatin, capcitabine, vinorelbine, and gemcitabine administered in the first and up to fifth-line setting have produced ORR between 24 and 81% in patients with HER-2/neu overexpressing MBC [74–80]. It is not known which agents comprise the optimal combination regimen. Selection of regimens is governed by the patient’s prior treatment history and the side effect profile of concurrent therapy. Patients who have achieved optimal clinical response to trastuzumab-based therapy may be considered for maintenance trastuzumab without concurrent chemotherapy, though the clinical benefits of this practice are not known.

**dosage and treatment schedule**

Currently, an initial loading dose of 4 mg/kg followed by 2 mg/kg weekly until disease progression is recommended. Other treatment regimens including the administration of a loading dose of 8 mg/kg followed by 6 mg/kg administered q. 21 days have been shown to have similar pharmacokinetics to weekly administration regimen [80, 81]. There are no data from controlled clinical trials to prove that these two schedules are equally effective. However, interim results from the HERA trial in the adjuvant setting do confirm that the latter dosing regimen is safe and more effective than not using trastuzumab.

**progressive disease during trastuzumab treatment**

There is currently no clinical evidence to support or reject the continued use of trastuzumab following progression of disease. This vexing question will achieve even greater importance because of the anticipated increased use of adjuvant and neoadjuvant trastuzumab in years to come.

**recommendation**

The use of first-line trastuzumab as either monotherapy or in combination with non-anthracycline-based chemotherapy was strongly recommended in patients with HER-2/neu protein overexpressing (3+ by IHC) or Her-2/neu FISH positive MBC regardless of age, prior adjuvant chemotherapy, or sites of metastatic disease. For patients with newly diagnosed MBC that is both hormone receptor positive and HER-2/neu positive, hormonal options should be explored first since there are no phase III data yet available confirming benefit with hormonal therapy plus trastuzumab.

**bisphosphonates: indication, choice of drugs and treatment duration**

Evidence from randomized clinical trials indicates that the use of bisphosphonates (90 mg pamidronate i.v. q. 21–28 days, 4 mg zolendronate i.v. q. 21–28 days, 6 mg ibandronate i.v. q. 21–28 days, ibandronate 50 mg p.o./day, 1600 mg clodronate p.o./day) in patients with bone metastases from MBC can reduce and delay the incidence of skeletal events [82]. Evidence supports the use of bisphosphonates be it with or without other anticancer treatment. Although most trials evaluated treatment given for about 2 years, no data are available on optimal duration of bisphosphonate treatment. There are insufficient data on the use of bisphosphonates in women without metastatic bone involvement or without tumor-induced hypercalcemia. Zoledronic acid has been shown to be superior to pamidronate in the treatment of hypercalcemia of malignancy [83].

The strongest evidence of efficacy is available for intravenous preparations, but there is no direct comparison between oral and intravenous preparations that suggests that oral bisphosphonates are inferior. Recently an uncommon toxicity, osteonecrosis of the jaw, has been reported after prolonged use of zoledronic acid or pamidronate. This toxicity may occur more frequently in women also undergoing dental procedures.

**supportive care**

**symptomatic anemia**

Anemia is common in patients with metastatic disease and may be caused or aggravated by cytotoxic treatment. Symptomatic anemia (with a hemoglobin below 11 g/dl) should be diagnosed, investigated and corrected. Considering various geographic approaches to the correction of symptomatic anemia, erythropoietin and erythrocyte transfusions are reasonable options. Although only few studies specifically dealt with MBC patients, supportive treatment with erythropoiesis stimulating proteins can be considered for the maintenance of quality of life in the case of symptomatic anemia including disease- or treatment-associated fatigue. For acute symptoms and in the
case of nonresponsiveness to erythropoiesis stimulating proteins, erythrocyte transfusions should be administered. In contrast, in patients undergoing cytotoxic treatment, erythropoiesis stimulating proteins should not be administered for the prevention of anemia or to reach high hemoglobin targets [84]. It is often difficult to clearly attribute fatigue and related symptoms to underlying disease, nutritional status, treatment side effects, psycho-oncologic disorders (e.g. depression) or to anemia. Comprehensive investigation of fatigue in patients with MBC should therefore take these considerations into account.

leukopenia
In the case of chemotherapy-associated myelosuppression or a history of recurrent febrile neutropenia following previous chemotherapy, the use of myeloid colony stimulating factors can be considered. If the anticipated febrile neutropenia rate is high (>20% according to NCCN guidelines, >40% according to ASCO guidelines [85, 86]), the primary prophylactic use of myeloid colony stimulating factors should be considered.

psychological support
Women with MBC frequently experience psychologic distress including depression, anxiety, stress-response syndrome, difficulty in coping and social isolation. Randomized trials of group psychosocial interventions in MBC identified psychological benefits including improvement in mood, pain control and coping. Based on these results, 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 of intervention, the optimal timing or the duration of such interventions. Furthermore, evidence of a survival advantage is not convincing.

hormone replacement therapy (HRT) and topical estrogen
Until the emergence of clear-cut data, the use of HRT in MBC is strongly discouraged, as HRT may stimulate growth of receptor-positive cancers. While the actual evidence about HRT use in patients suffering from MBC is currently limited, it has been reported that its withdrawal could prove therapeutic. There have been several reports of tumor responses following HRT withdrawal [87, 88]. However, there appears to be less rationale for prohibiting HRT use in patients with receptor-negative MBC. Recently, the topical (vaginal) use of estrogens was questioned with respect to its potential impact on systemic estrogen levels. This may impair aromatase inhibitor treatment for patients with breast cancer. If topical estrogens need to be considered for quality-of-life reasons, preparations should be chosen that result in the lowest possible systemic absorption. Vaginal estradiol tablets should be used with caution in MBC patients; therapy using estril suppositories may be less concerning [89].

emerging treatments and future directions
It was acknowledged that a rapidly increasing number of molecular structures of malignant cells can be targeted by various agents including signal transduction inhibitors, monoclonal antibodies, anti-cancer vaccines, antisense strategies or anti-angiogenic drugs. As the mode of action of the various available agents is completely different from cytotoxic treatment, biologic modulators represent ideal combination partners for chemotherapeutic agents. Based upon these considerations, a series of emerging treatments with promising efficacy can be identified, whereas other strategies might gain importance in the future.

emerging treatments
bevacizumab (Avastin®). Bevacizumab is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF) and is the most mature therapeutic agent specifically designed to disrupt angiogenesis. Several phase II trials of bevacizumab alone or in combination with chemotherapy have demonstrated efficacy with a low toxicity profile in patients with metastatic breast cancer [90]. Further evidence of bevacizumab’s efficacy in breast cancer was presented in two randomized phase III trials. In one trial, including heavily pretreated patients with MBC bevacizumab plus capecitabine was compared to chemotherapy alone [91]. Although response rates increased substantially in the bevacizumab arm, the responses did not translate into prolonged progression-free survival or overall survival. In contrast to these data, initial results of another phase III trial in women with previously untreated metastatic breast cancer, show that the addition of bevacizumab to weekly paclitaxel does increase progression-free survival and overall survival [92]. Ongoing studies aim to confirm these data and optimize dose and schedule of bevacizumab therapy.

lapatinib. Several tyrosine kinase inhibitors (TKI) are being investigated in phase II trials in metastatic breast cancer. Encouraging data have been reported for lapatinib, a TKI directed both against the erbB1 and the erbB2 (HER-2) receptor [93–95]. In a recently reported phase II trial, lapatinib was tested as first-line therapy for breast cancer patients with tumors that express large amounts of erbB2. The drug was well tolerated and a clinical response rate of 38% was achieved [96]. In contrast to monoclonal antibodies such as trastuzumab, this drug can be given orally. However, further clinical trials are required to confirm these initial data.

future directions
Proper definition of targets, mechanisms of drug sensitivity and resistance, patients and endpoints is necessary for future clinical trials including those evaluating the therapeutic potential of established drugs such as anthracyclines (e.g. expression of topoisomerase 2) and trastuzumab. Given the recent introduction of many new treatments for advanced breast cancer, it is expected that much progress will be made over the next 5 to 10 years.

Specific recommendations for future trials include:
• investigation of target expression by biopsy or fine needle aspiration before start of therapy,
• investigation of biomarkers such as functional imaging, biopsies, proteomics, etc.
• consideration of ‘multiple hits’ to achieve best results from signal transduction inhibitors due to cross-talk [97],
• linkage of translational research programs to early clinical trials investigating targeted therapy,
• combination with conventional treatment may be the most successful approach, but requires careful design.

The establishment of tissue banks for frozen tumor samples and serum banks for future analysis of biologic tumor characteristics was strongly encouraged.

**appendix: participants and affiliations (in alphabetical order)**

- Semir Beslija Institute of Oncology, Sarajevo, Bosnia and Herzegovina
- Jacques Bonneterre, Centre Oscar Lambret, Lille, France
- Harold J. Burstein, Dana-Farber Cancer Institute, Boston, USA
- Veronique Cocquyt, Oncologisch Centrum, Universiteit Ziekenhuis, Gent, Belgium
- Michael Gnant, Department of Surgery, Medical University of Vienna, Austria
- Pamela Goodwin, Samuel Lunenfeld Research Institute, Mount Sinai Hospital, Toronto, Canada
- Volker Heinemann, Klinikum Groβhadern, Munich, Germany
- Jacek Jassem, Department of Oncology and Radiotherapy, Medical University, Gdansk, Poland
- Wolfgang J. Köstler, Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria
- Michael Krainer, Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria
- Silvie Menard, Istituto Tumori, Milan, Italy
- Thierry Petit, Centre Paul Strauss, Strasbourg, France
- Lubos Petruzelka, Oncology Department, Charles University, Prague, Czech Republic
- Kurt Possinger, Med. Klinik der Charite, Berlin, Germany
- Edward Stadtmauer, University of Pennsylvania Cancer Center, Philadelphia, USA
- Peter Schmid, Charing Cross Hospital, Imperial College, London, United Kingdom
- Martin Stockler, Sydney Cancer Centre RPA and Concord Hospitals, University of Sydney, Camperdown NSW, Sydney, Australia
- Simon Van Belle, Oncologisch Centrum, Universitair Ziekenhuis, Gent, Belgium
- Charles Vogel, Cancer Research Network, Inc. Plantation, Florida, USA
- Nicholas Wilcken, Dept. of Medical Oncology and Palliative Care, Westmead Hospital, Sydney, Australia
- Christoph Wiltschke, Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria
- Christoph C. Zielinski, Clinical Division of Oncology, Department of Medicine I, Medical University of Vienna, Austria
- Heinz Zwierzina, Dept. Medicine, Medical University of Innsbruck, Austria

**acknowledgements**

The panelists thank Ms Ursula Fischer for the organization of the infrastructure of the conference. The conference was made possible by unrestricted educational grants from the following companies: Amgen, Boehringer Ingelheim, Eli Lilly, Roche.

**references**


