Treatment of metastatic breast cancer: second line and beyond

H. Roché & L. T. Vahdat

Department of Medical Oncology, Institut Claudius Regaud, Toulouse, France; Department of Medical Oncology, Weill-Cornell Breast Cancer Center, New York, USA

Received 25 November 2009; revised 25 June 2010; accepted 1 July 2010

Increasing use of standard chemotherapy, especially anthracycline- and taxane-based therapies, in early-stage breast cancer has led to an increase in heavily pretreated and/or treatment-resistant cases of metastatic breast cancer (MBC). Thus, second and later lines of MBC therapy frequently involve the clinically challenging picture of progressive disease and limited treatment options. While several prognostic factors have been identified to aid treatment selection in MBC patients, treatment is palliative and aimed at prolonging survival, controlling symptoms, and maximizing patients’ quality of life. No globally accepted standard exists for meeting these goals, and treatment patterns vary according to region. The list of available agents for the treatment of MBC is increasing with newer chemotherapeutic agents and molecular-targeted therapies. Within recent years, several single-agent and combination chemotherapy regimens have been shown to improve progression-free survival and reduce symptoms of disease in clinical studies in patients with resistant and/or heavily pretreated MBC. However, at present, the demonstrated benefits of these medical interventions have usually not included extension of overall survival times. It is hoped that in the near future, ongoing refinements to treatment approaches used in second-line settings and beyond will allow meaningful improvements in symptom control and survival in MBC.

Key words: breast neoplasms, chemotherapy, drug resistance, metastasis, targeted therapies, treatment outcome

introduction

Despite the many advances that have been achieved in the treatment of breast cancer, the diagnosis of patients with metastatic breast cancer (MBC) remains poor, with a median survival of 2–4 years [1]. In the United States, it is estimated that >40,000 women died as a result of breast cancer in 2008, making it the second leading cause of cancer-related death among women after lung cancer [2]. In Europe, breast cancer has overtaken lung cancer as the most common cancer diagnosed, with 429,900 new cases in 2006 (13.5% of all cancer cases). It is the third most common cause of cancer death among Europeans in general, after lung and colorectal cancers [3].

While <10% of newly diagnosed patients present with locally advanced or metastatic disease [4], ~30% to 50% of patients diagnosed at earlier stages will subsequently develop metastatic disease, despite the use of endocrine and chemotherapy adjuvant therapies [2]. Breast cancer is considered incurable following metastasis, and therapeutic goals are palliative in nature. Moreover, earlier and more aggressive use of cytotoxic regimens has increased the incidence of treatment-resistant metastatic disease.

A rapidly growing pool of effective treatment options for MBC has increased response rates, progression-free survival (PFS), and/or overall survival (OS) [5, 6]. The taxanes, trastuzumab, vinorelbine, and capecitabine were introduced in the mid-to-late 1990s, and the last decade has seen the introduction of anastrozole, letrozole, exemestane, fulvestrant, gemcitabine, ixabepilone, nanoparticle albumin-bound paclitaxel (nab-paclitaxel), bevacizumab, and lapatinib. The taxanes and capcitabine have been among the most successful agents against MBC, having demonstrated activity alone and in combination with several other agents. Ixabepilone, the first of a new class of microtubule-stabilizing agents called the epothilones, was approved in the United States in 2007. Hormonal therapies, such as the antiestrogen tamoxifen and the aromatase inhibitors, tend to have a lesser role in advanced disease, as endocrine resistance is common and/or hormone receptivity decreases over the course of the disease. The introduction of trastuzumab, an antibody directed against the human epidermal growth factor receptor-2 (HER2) protein, heralded with success, the birth of targeted molecular therapy against breast cancer. The dual kinase inhibitor lapatinib has a broader specificity and is effective in HER2-positive patients.

*Correspondence to: Dr H. Roché, Department of Medical Oncology, Institut Claudius Regaud, 20-24 rue du Saint Pierre, 31052 Toulouse cedex, France. Tel: +33-561424130; Fax: +33-561424623; E-mail: roche.henri@claudiusregaud.fr

© The Author 2010. Published by Oxford University Press on behalf of the European Society for Medical Oncology. All rights reserved. For permissions, please email: journals.permissions@oxfordjournals.org
who have experienced resistance to trastuzumab. Bevacizumab, more recently, has opened the door to angiogenic agents.

No global consensus exists regarding the ideal treatment strategy for MBC, and no guidelines are available. The selection of treatment depends on several factors, including patient and tumor characteristics, aggressiveness of the disease, response to previous therapies, time since last exposure, agents used in the past, and cumulative doses [7]. Availability and regulatory approval of various anticancer agents, along with regional diversity regarding what is expected from therapy, further diversify treatment patterns in various parts of the world.

Ideally, MBC therapy is highly individualized, and oncologists rely on clinical trial data to make decisions regarding which therapy is likely to be most beneficial. In clinical practice, however, many women with MBC do not fit the profile of clinical trial participants, and when assessing the implications of trial findings, it is important for oncologists to be familiar with the clinical setting in which they were obtained.

In addition, cost considerations such as those related to patients’ finances, physician reimbursement, and government-regulated drug programs may affect treatment selection. The financial impact of breast cancer can be large, even among those with health insurance, and affected patients are at increased risk of financial hardship. In a survey of USA cancer patients, out-of-pocket expenditures (mostly copayments for hospitalizations and physician visits) and lost income costs averaged $1455/month, accounting for 98% of income among the lowest household income range [8]. Although a physician’s decision to administer chemotherapy was not measurably affected by higher reimbursement, providers who were more generously reimbursed prescribed more costly chemotherapy regimens to MBC patients [9]. Disparities in rates of reimbursement seemed to favor the use of older and sometimes outdated procedures over less invasive operations that produce better outcomes [10]. In Europe, the majority of the cancer therapy costs fall on third-party payers, usually the government or sickness funds. Drug budgets are regulated in most European countries, with reimbursement decisions involving reference pricing and cost-effectiveness considerations. Nevertheless, studies have shown a wide variation in access to cancer drugs among the various countries in Europe [11]. Differences in approval and labeling among national drug regulatory agencies may help to further explain this variation.

Such factors compound the difficulty that oncologists face when deciding which patient should receive which therapy following failure of first-line treatment of metastatic disease. To aid physicians in weighing the available options for second-line and subsequent treatment of MBC, the aim of this article is to review these options, with an emphasis on newer agents that have shown efficacy after failure of anthracyclines and taxanes (Table 1) [12–19].

treatment strategy

Patients with MBC represent a heterogeneous group, and thus, an individualized approach to therapy is essential. As in earlier stages of disease, the goals of treatment in the second-line setting and beyond remain straightforward to obtain maximum control of symptoms, prevent serious complications, and increase survival without diminishing quality of life.

First-line treatment recommendations exist for the main tumor categories, and these guidelines are more or less standard [e.g. targeted therapies for estrogen receptor (ER)- and HER2-positive disease]. In patients who do not show progression after first-line treatment, maintenance chemotherapy is a rational approach that prolongs time to progression (TTP). However, the optimal duration of chemotherapy treatment of MBC remains a matter of debate; no consistent improvements in OS have been demonstrated [20].

In addition, the issue of whether to employ combination therapy or to continue with monotherapy until it is no longer effective also remains unresolved. Increasing evidence has revealed an efficacy advantage for doublet therapy, although an improvement in survival remains elusive. In addition to the individual agents used, administration choices (sequential versus combination therapy and continuous versus intermittent treatment) can also influence response rates.

When selecting therapy, the clinician should also consider practical aspects, such as the need for hospitalization and the patient’s willingness to comply with the regimen. A major ongoing challenge is the incorporation of novel biological agents into practical treatment schedules for advanced breast cancer in order to maximize their therapeutic potential. In many cases, data for use of these agents in second-line treatment of MBC are not yet available, and decisions are made based on personal preference of the clinician in consultation with the patient.

Once first-line treatment of MBC has failed, management becomes even more challenging. The likelihood of response subsequently decreases by approximately one-half with each prior regimen the patient has received as either adjuvant or MBC treatment. Response rates may be as high as 60%–80% with first-line treatment in patients who have not received adjuvant therapy and are ~30% and 15%, respectively, in patients who have received two or three prior regimens [7].

Ideally, then, heavily pretreated patients need treatments that do not contribute to cumulative toxicity and do not exhibit cross-resistance with agents previously used. The presence of ER and/or progesterone receptor (PR) is strongly predictive of a response to hormone therapy, but it is not clear if this advantage is maintained in later stages [21]. Patients with no symptomatic visceral disease may undergo up to three endocrine regimens [22] (Table 1), but since most tumors eventually develop resistance to endocrine therapies, use of these agents in later-line settings is limited. Clearly, more options are needed for the treatment of MBC, particularly for second-line and subsequent therapy, and several potential regimens are under investigation in this clinical setting (Table 2).

second-line cytotoxic chemotherapy

Cytotoxic chemotherapy is indicated for patients with symptomatic visceral disease or in whom there is no clinical benefit after three consecutive endocrine regimens [22]. If there is no response to three sequential cytotoxic regimens or Eastern Cooperative Oncology Group performance status is greater
Table 1. Overview of recently developed treatment options for second- and subsequent-line treatment of MBC

<table>
<thead>
<tr>
<th>Drug</th>
<th>Class</th>
<th>$N$</th>
<th>Responses, median</th>
<th>Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>United States$^a$</td>
</tr>
<tr>
<td>Endocrine therapy</td>
<td></td>
<td></td>
<td></td>
<td>Treatment of hormone receptor-positive MBC in postmenopausal women with disease progression following antiestrogen therapy</td>
</tr>
<tr>
<td>Fulvestrant [12]</td>
<td>Pure ER antagonist; competitively inhibits the binding of natural estradiol</td>
<td>428 (fulvestrant)</td>
<td>TTP: 5.5 versus 4.1 months $P = NS$, ORR: 19.2% versus 16.5% $P = NS$</td>
<td>Treatment of advanced breast cancer in postmenopausal women whose disease has progressed following tamoxifen therapy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>423 (anastrozole)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exemestane [13]</td>
<td>Aromatase inactivator; prevents conversion of androgens to estrogens</td>
<td>366 (exemestane)</td>
<td>TTP: 20.3 versus 16.6 weeks $P = 0.037$, ORR: 15.0 versus 12.4 $P = NS$, OS: not reached versus 123.4 weeks $P = 0.039$</td>
<td>Treatment of HER2-overexpressing breast cancer in patients who have received at least two chemotherapy regimens for metastatic disease (including at least an anthracycline and a taxane, unless contraindicated; hormone receptor-positive patients must also have failed hormonal therapy) In combination with paclitaxel: treatment of HER2-overexpressing MBC</td>
</tr>
<tr>
<td></td>
<td></td>
<td>403 (megestrol acetate)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Targeted therapy</td>
<td></td>
<td></td>
<td></td>
<td>Monotherapy: treatment of HER2-overexpressing breast cancer in patients who have received one or more chemotherapy regimens for metastatic disease In combination with paclitaxel: treatment of HER2-overexpressing MBC</td>
</tr>
<tr>
<td>Trastuzumab [14]</td>
<td>Monoclonal antibody that blocks signaling through HER2</td>
<td>235 (chemotherapy$^c$ + trastuzumab) 234 (chemotherapy$^c$ alone)</td>
<td>TTP: 7.4 versus 4.6 months ($P &lt; 0.001$), ORR: 50% versus 32% ($P &lt; 0.001$), OS: 25.1 versus 20.3 months ($P = 0.046$)</td>
<td></td>
</tr>
<tr>
<td>Drug</td>
<td>Class</td>
<td>N</td>
<td>Responses, median</td>
<td>Indications United Statesa</td>
</tr>
<tr>
<td>------</td>
<td>-------</td>
<td>-------</td>
<td>-------------------</td>
<td>-----------------------------</td>
</tr>
<tr>
<td><strong>Lapatinib [15]</strong></td>
<td>Small molecule inhibitor of EGFR and HER2</td>
<td>163 (lapatinib + capecitabine), 161 (capecitabine)</td>
<td>TtP: 8.4 versus 4.4 months ($P &lt; 0.001$), ORR: 22% versus 14% ($P = 0.09$), OS = NS</td>
<td>In combination with capecitabine for the treatment of patients with advanced or MBC whose tumors overexpress HER2 and who have received prior therapy including an anthracycline, a taxane, and trastuzumab</td>
</tr>
<tr>
<td><strong>Cytotoxic therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Capecitabine [16]</strong></td>
<td>Antimetabolite; prodrug for 5-fluorouracil</td>
<td>255 (capecitabine + docetaxel) 256 (docetaxel)</td>
<td>TtP: 6.1 versus 4.2 months ($P = 0.0001$), ORR: 42% versus 30% ($P = 0.006$), OS: 14.5 versus 11.5 months ($P = 0.0126$)</td>
<td>Monotherapy: treatment of patients with MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or resistant to paclitaxel and for whom further anthracycline therapy is not indicated</td>
</tr>
<tr>
<td><strong>Ixabepilone [17, 18]</strong></td>
<td>Epothilone; microtubule-stabilizing agent</td>
<td>369 (ixabepilone + capcitabine) 368 (capcitabine)</td>
<td>PFS: 5.3 versus 3.8 months ($P = 0.0011$), ORR: 42% versus 23% ($P &lt; 0.0001$), OS = NS</td>
<td>Monotherapy: treatment of metastatic or locally advanced breast cancer in patients after failure of an anthracycline, a taxane, and capcitabine</td>
</tr>
</tbody>
</table>
than or equal to three, palliative care with no further cytotoxic therapy may be considered [22].

The cytotoxic chemotherapy options for second- and subsequent-line chemotherapy have expanded in the last decade (see Table 1). The development of such agents and identification of genetic biomarkers in translational studies offer the potential to improve prospects for the management of MBC.

taxanes

Until recently, the taxanes (in particular docetaxel) were considered to be the most effective second-line treatment of MBC in patients failing anthracycline treatment [23]. A randomized multicenter phase III study compared docetaxel 100 mg/m² and paclitaxel 175 mg/m² (on day 1 in 21-day cycles) in 449 patients with advanced breast cancer that had progressed after anthracycline-based chemotherapy [24]. Docetaxel was the superior taxane monotherapy in terms of median TtP (5.7 versus 3.6 months with paclitaxel; \( P < 0.0001 \)) and OS (15.4 versus 12.7 months; \( P = 0.03 \)), although treatment-related toxic effects were more common in docetaxel recipients. Unfortunately, no studies have directly compared docetaxel with weekly paclitaxel. In other phase III studies of women with MBC who had failed previous treatment with anthracycline in the adjuvant or metastatic setting, docetaxel was superior to mitomycin C plus vinblastine [25] and to sequential methotrexate and fluorouracil [26]. In both of these studies, response rates and TtP with docetaxel were approximately double than those measured in the comparator arms.

Cross-resistance between paclitaxel and docetaxel is significant but not complete. Docetaxel was marginally effective when given to paclitaxel-resistant patients with MBC, yielding a median TtP of 10 weeks and 1 complete response among 44 assessable patients. Interestingly, docetaxel yielded a clinical benefit only in patients who had received prior paclitaxel as 1- or 3-h infusions, not in those who had received 24-h infusions [27].

nanoparticle albumin-bound paclitaxel

To mitigate toxic effects, notably the severe hypersensitivity associated with the polyethylated castor oil used in conventional taxane formulations, a nanoparticle albumin-bound formulation of paclitaxel (nab-paclitaxel) has been developed [28]. In both the United States and Europe, nab-paclitaxel is approved for the treatment of breast cancer after failure of combination chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy. Prior therapy should have included an anthracycline unless contraindicated.

Clinical studies to date indicate that nab-paclitaxel is more effective and better tolerated than conventional paclitaxel. Nab-paclitaxel (260 mg/m² every 3 weeks) and conventional paclitaxel (175 mg/m² every 3 weeks) were compared in a phase III study in 460 patients with MBC who had not received a taxane for their metastatic disease and had not relapsed within 1 year of adjuvant taxane treatment. Fifty-nine percent of patients who had progressed after first-line therapy for MBC [29]. Response rates were significantly higher with nab-paclitaxel than with conventional paclitaxel (33% vs 19%; \( P = 0.001 \));
in second- or subsequent-line patients, response rates were 27% versus 13%, respectively, \( P = 0.006 \). Median TtP was significantly longer with nab-paclitaxel than with conventional paclitaxel; in second- or subsequent-line patients, TtP was 20.9 versus 16.1 weeks, respectively (\( P = 0.02 \)). In addition, the incidence of grade 4 neutropenia was significantly lower with nab-paclitaxel (9% versus 22%).

### Capecitabine

Capecitabine is a valuable second-line treatment option for MBC that is approved in both the United States and Europe. The major advantage of the drug is its oral administration, which allows treatment at home. Capecitabine as monotherapy is indicated for the second- and subsequent-line treatment of patients with MBC resistant to both paclitaxel and an anthracycline-containing chemotherapy regimen or in patients resistant to paclitaxel and for whom further anthracycline therapy is not indicated. In noncomparative phase II trials of capecitabine monotherapy in patients with MBC previously treated with anthracyclines and/or taxanes, response rates were 15%–28%, TtP was 3–5 months, and OS was 10–15 months [30–33]. Capecitabine is well tolerated with minimal myelosuppression and alopecia, but it is associated with diarrhea and hand–foot syndrome [30–33].

The combination of capecitabine and docetaxel is indicated for the treatment of patients with MBC after failure of first-line anthracycline-containing chemotherapy. A phase III study in 511 women with locally advanced or MBC that recurred after anthracycline treatment compared capecitabine plus docetaxel with docetaxel alone [16]. The median TtP was significantly prolonged to 6.1 months with capecitabine plus docetaxel compared with 4.2 months with docetaxel alone \( (P = 0.0001; \text{hazard ratio (HR)}, 0.652; 95\% \text{ confidence interval (CI)} 0.545–0.780) \). Median OS was also significantly prolonged (14.5 versus 11.5 months; \( \text{HR}, 0.775; 95\% \text{ CI} 0.634–0.947; P = 0.0126 \)). In addition, response rates were higher with combination therapy versus docetaxel alone (42% versus 30%; \( P = 0.006 \)). Although the toxicity profile of the regimen was manageable, the incidence of gastrointestinal adverse effects and hand–foot syndrome was higher with combination therapy.

### Gemcitabine

The combination of gemcitabine and paclitaxel has received regulatory approval in both the United States and Europe for first-line use in MBC after failure of anthracycline-containing adjuvant therapy [34]. Second-line treatment of MBC with gemcitabine in combination with docetaxel is being investigated.

Gemcitabine plus docetaxel (GD) was compared with capecitabine plus docetaxel (CD) in a phase III study in 305 women with locally advanced or MBC who had received treatment with at least one prior anthracycline regimen in the

<table>
<thead>
<tr>
<th>NCT Identifier*</th>
<th>Study drugs and trial design</th>
<th>Primary outcome measure</th>
<th>Sponsors and collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT00637325</td>
<td>Trastuzumab weekly (2 mg/kg) or a 3 weekly (6 mg/kg) in patients progressing after first-line chemotherapy containing trastuzumab</td>
<td>PFS, OS</td>
<td>Regione LombardiaMario Negri Institute for Pharmacological ResearchIstituto Clinico Humanitas</td>
</tr>
<tr>
<td>NCT004448279</td>
<td>Trastuzumab plus chemotherapy as prescribed versus chemotherapy alone in patients progressing after first-line chemotherapy containing trastuzumab</td>
<td>TtP and PFS after discontinuing trastuzumab, respectively</td>
<td>Hoffmann-La Roche</td>
</tr>
<tr>
<td>NCT00684216</td>
<td>Capecitabine 200 mg b.i.d followed by hormonal therapy versus the reverse order in patients with ER-positive MBC</td>
<td>QOL during study period</td>
<td>The Netherlands Cancer Institute</td>
</tr>
<tr>
<td>NCT00635713</td>
<td>Fulvestrant 125 mg and anastrozole 1 mg versus fulvestrant 250 mg and anastrozole 1 mg in postmenopausal women</td>
<td>TtP</td>
<td>AstraZeneca</td>
</tr>
<tr>
<td>NCT00388726</td>
<td>Eribulin mesylate versus physician’s choice, including supportive care only, in MBC treated with 2–5 prior lines of therapy including anthracycline and taxane</td>
<td>OS</td>
<td>Eisai</td>
</tr>
</tbody>
</table>

*www.clinicaltrials.gov.

ER, estrogen receptor; MBC, metastatic breast cancer; OS, overall survival; PFS, progression-free survival; QOL, quality of life; TtP, time to progression.
months, taxane improved PFS over vinorelbine alone (6.0 versus 4.0 months, P = 0.059). In the subgroup receiving second-line metastatic treatment (n = 107), median PFS was 6.6 months (95% CI 5.09–8.41) for GD and 8.5 months (95% CI 6.70–9.79) for CD. Severe nonhematologic toxic effects were significantly higher in the CD arm, including diarrhea, hand–foot syndrome, and mucositis.

The addition of gemcitabine to vinorelbine therapy in 252 women with MBC previously treated with an anthracycline and taxane improved PFS over vinorelbine alone (6.0 versus 4.0 months, P = 0.0028), but the incidence of grade 3 or 4 neutropenia was significantly increased with combination therapy [36]. Gemcitabine continues to be explored as part of combination therapy, and it is also frequently used as monotherapy in MBC. Available data suggest that the antitumor activity of single-agent gemcitabine is probably low compared with that of single-agent taxanes or anthracyclines, at least in MBC; however, because it is well tolerated by most patients, gemcitabine monotherapy remains a frequently employed treatment plan in this palliative setting [37].

ixabepilone

Ixabepilone is the first of a new class of antineoplastic agents, the epothilones. Ixabepilone is approved in the United States (but not in Europe) in combination with capecitabine for the treatment of metastatic or locally advanced breast cancer after failure of an anthracycline and a taxane [38]. As monotherapy, ixabepilone is also approved in the United States for the treatment of metastatic or locally advanced breast cancer after failure of an anthracycline, a taxane, and capcitabine [38].

Although ixabepilone is a microtubule stabilizer and induces apoptosis—features shared with the taxanes—ixabepilone’s tubulin-binding properties and apoptotic mechanisms are distinct from those of taxanes. Ixabepilone has low susceptibility to multiple mechanisms of tumor cell resistance that commonly reduce the efficacy of taxanes and anthracyclines [39, 40]. Ixabepilone has shown strong preclinical activity against a wide range of tumor types, including both drug-sensitive tumors and those resistant to various agents, including taxanes and/or anthracyclines, and these findings have translated to the clinical setting [17, 41, 42].

A pivotal phase II study evaluated ixabepilone monotherapy in 126 women with MBC or locally advanced breast cancer resistant to anthracyclines, taxanes, and capecitabine [43], 88% of whom had received at least two prior treatment regimens for metastatic disease. In this population, 100%, 98%, and 38% of tumors were resistant to capecitabine, taxanes, and anthracyclines, respectively. Investigator-assessed response rates were 18.3% (11.5% by independent radiology review), median PFS was 3.1 months, and OS was 8.6 months.

The combination of ixabepilone plus capecitabine was compared with capecitabine alone in two large phase III studies in a total of 1973 women with locally advanced or MBC pretreated with anthracyclines or taxanes. In both trials, ixabepilone plus capecitabine was superior to capecitabine alone in terms of PFS and response rates [17, 18]. The results in patients who met the strict definition of resistance (n = 1337) were very similar to those of the overall patient population: addition of ixabepilone to capecitabine prolonged median PFS (5.1 versus 3.7 months; HR, 0.81; 95% CI 0.72–0.91) and increased overall response rate (ORR; 39% versus 22%) over capecitabine alone [44]. In various other subgroup analyses of these two studies, ixabepilone plus capecitabine was superior to capecitabine alone in a range of important patient subgroups with unfavorable prognostic, including HER2-positive disease [45], ER-negative disease [46], ‘triple-negative’ (ER-, PR-, and HER2-negative) disease [47], and symptomatic patients [48].

vinorelbine

The vinca alkaloid vinorelbine is being investigated as a salvage treatment in MBC, having received Europe approval in this setting (but not USA approval). Vinorelbine monotherapy in patients with advanced or MBC after failure of anthracyclines and/or taxanes has produced widely varying results, with response rates ranging from 25% to 46%, TtP of 3 months, PFS of 4 months, and OS of 6 to 16 months [36, 49, 50].

Vinorelbine in combination with cisplatin has shown activity in patients with MBC previously treated with anthracyclines and/or taxanes in the adjuvant or metastatic setting, with response rates in the range of 40%–50%, median TtP of 4–5 months, and OS of 6–12 months [51–53]. Notably, none of these trials were placebo controlled. In a phase III trial in patients with MBC after failure of anthracycline therapy in the adjuvant or metastatic setting, vinorelbine plus 5-fluorouracil (5-FU) had similar efficacy to docetaxel [54]. Median TtP was 5.1 months with vinorelbine/5-FU versus 6.5 months with docetaxel and response rates were 39% and 43%, respectively. These differences were not significant; however, docetaxel was the better-tolerated treatment.

Oral vinorelbine administered on a weekly schedule has also proven to be effective and well tolerated for first-line treatment of locally advanced or MBC and offers a valuable alternative to the i.v. route [55, 56].

other agents

Several other agents traditionally included in cytotoxic regimens are used in various combination regimens in the management of MBC, particularly in women whose disease has progressed after chemotherapy with anthracyclines and taxanes. These agents include 5-FU, vinblastine, methotrexate, mitomycin C, and platinum agents. Controlled trials in this setting are limited, and clinical studies continue to evaluate potential application of established therapies.

Novel approaches to dose schedules and combinations of agents have generated improvements in some long-standing treatment options. For example, initial data regarding metronomic chemotherapy indicate that continuous low-dose cyclophosphamide and methotrexate are minimally toxic and effective in heavily pretreated breast cancer patients [20]. Likewise, anthracycline- and taxane-pretreated patients in a phase I dose-finding trial seemed to tolerate continuous vinorelbine (60 mg) three times a week in combination with capecitabine (1250 mg/m² twice a day) [37].

In addition, ongoing trials in women with previously treated MBC are currently investigating the utility of alternative
combinations of the agents above, as well as for new formulations of existing agents, such as nonpegylated liposomal doxorubicin. Agents in entirely new classes, such as the halichondrin B derivative eribulin, are also showing some promise in patients who have already progressed on other therapies. Eribulin targets microtubule structures, but by a mechanism that is distinct from that of taxanes or epothilones. In a phase II study, eribulin demonstrated an ORR of 11.5% in a taxane- and anthracycline-pretreated population of women with MBC [58]. A phase III investigation of this agent has recently been completed and data are expected shortly.

**second-line targeted therapy**

HER2 receptors are present in 20%–30% of metastatic breast tumors [18] and are associated with more aggressive disease [21]. The presence of HER2 receptors has been shown to predict response to trastuzumab in the metastatic setting [21], and several targeted therapies have been evaluated in this indication.

**trastuzumab**

Trastuzumab, a monoclonal antibody targeting HER2, is now the standard of care for first-line treatment in combination with a taxane for HER2-positive MBC [59]. In addition, monotherapy with trastuzumab is indicated for HER2-positive MBC in patients who have received one or more chemotherapy regimens for MBC.

A phase II noncomparative trial evaluated trastuzumab monotherapy in 222 women with HER2-overexpressing MBC who had progressive disease after one or two cytotoxic chemotherapy regimens for MBC [60]. Trastuzumab produced an ORR of 15%; median OS was 13 months. Trastuzumab tended to be more effective in patients with high (level ≥3) HER2 overexpression. The most clinically significant adverse effect was cardiotoxicity, with an incidence of 4.7%, warranting caution in patients who have already received a high cumulative dose of anthracyclines.

In a recent phase III study, 156 patients with HER2-positive locally advanced or MBC that had progressed during treatment with trastuzumab (48% of whom had received anthracycline chemotherapy) were randomized to treatment with capecitabine monotherapy or capecitabine in combination with continued trastuzumab [61]. Preliminary results indicate that patients continuing trastuzumab had higher crude response rate (49% versus 25%) and lower rate of primary progression (16% versus 26%) but similar survival; the regimens had equivalent toxic effects.

Studies continue to address the question of whether to continue trastuzumab during subsequent lines of chemotherapy following recurrence after first-line trastuzumab therapy. A systematic review of observational analyses of this question revealed that responses to a second line of trastuzumab therapy were lower than first responses but still promising (relative ORR of 33% and 59% and respective clinical benefits of 62% and 83%) [62]. In another retrospective study, patients who continued trastuzumab therapy beyond disease progression (administered concurrently with one to two additional lines of chemotherapy) exhibited better response rates than those who halted trastuzumab (35% versus 16%, respectively). No significant differences in OS were observed [63]. In another study, however, patients who continue trastuzumab therapy following development of brain metastases experienced longer disease-free survival compared with those who receive no further trastuzumab therapy after being diagnosed with brain metastases [64]. In the future, randomized data may answer whether continuation of trastuzumab beyond progression is a viable treatment choice compared with other available options.

**lapatinib**

The dual epidermal growth factor receptor and HER2 inhibitor lapatinib is specifically indicated for use in combination with capecitabine in patients with HER2-positive advanced or MBC who have previously received an anthracycline, a taxane, and trastuzumab. A phase III study in 324 patients compared lapatinib plus capecitabine with capecitabine alone in HER2-positive locally advanced, or MBC that had progressed after treatment with regimens that included an anthracycline, a taxane, and trastuzumab [15]. Previous therapies had to include, but were not limited to, at least four cycles of a regimen that included an anthracycline and a taxane (two cycles if the disease progressed while the patient was receiving therapy) administered concurrently or separately as adjuvant therapy or for metastatic disease. Previous treatment with trastuzumab was also required (alone or in combination with chemotherapy) for locally advanced or metastatic disease [15]. The median TTP was 8.4 months with lapatinib plus capecitabine versus 4.4 months with capecitabine alone (HR, 0.49; 95% CI 0.34–0.71; P < 0.001), and response rates were, retrospectively, 22% versus 14% (P = 0.09). The addition of lapatinib did not prolong OS [15]. Compared with capecitabine alone, the combination regimen was not associated with an increase in serious adverse effects. Unfortunately, a direct comparison between trastuzumab and lapatinib as second-line treatment is not available.

In Europe and the United States, the approved schedules for lapatinib and capecitabine are daily for 21 days and daily for 14 days with a 7-day break, respectively. However, preliminary evidence suggests that administering capecitabine daily for 7 days with a 7-day break may be better tolerated and perhaps more efficacious than the approved dose, which has led to a phase II evaluation of this capecitabine schedule in combination with lapatinib in HER2-positive trastuzumab-resistant patients with MBC. The regimen appears to be well tolerated, and further data are forthcoming this year [65].

**bevacizumab**

In MBC, the vascular endothelial growth factor inhibitor bevacizumab is currently approved in the United States and Europe only, together with paclitaxel, as first-line therapy for HER2-negative patients. The current USA labeling specifically contraindicates bevacizumab for patients who had progressed on anthracycline- and taxane-based therapy for MBC, based on the findings of a large phase III trial in which addition of
bevacizumab to capecitabine failed to improve PFS or OS over capecitabine alone (4.86 versus 4.17 months, respectively; HR, 0.98) [66]. However, more recent data from the RIBBON-2 trial suggest that this agent may have a place in second-line therapy [67]. In this phase III study, bevacizumab was evaluated in a less heavily pretreated population (only one prior treatment of MBC) in combination with capecitabine or various other chemotherapies, including taxanes (standard or nab-paclitaxel or docetaxel), gemcitabine, or vinorelbine. In contrast to the earlier study, adding bevacizumab to chemotherapy improved PFS from 5.1 to 7.2 months (HR, 0.78; \( P = 0.0072 \)). Whether bevacizumab has a viable place in later-line therapy for MBC remains to be clarified.

conclusions

A substantial proportion of patients with breast cancer eventually progress to metastatic disease. MBC has multiple clinical presentations and treatment should be selected according to the patient’s tumor characteristics, treatment history, and performance status [7]. The increased use of anthracyclines and taxanes in the earlier stages of disease makes treatment selection in the second- and later-line settings more challenging, and drug resistance often limits therapeutic options. A number of issues relating to second-line treatment of MBC await clarification in clinical studies, including dosing strategies and the best way to incorporate newer agents. Several agents have clearly improved outcome either as monotherapy or in combination regimens, in the sequential treatment of patients with MBC. Further investigation of new and established drug therapies for breast cancer is enabling better definition of therapeutic targets, mechanisms of drug sensitivity and resistance, patients, and therapy end points. Several emerging drug therapies have demonstrated promise in patients with MBC, and further progress in medical management is expected in the coming years. It is hoped that the judicious use of novel and standard therapies will allow continued improvements in the management of patients with MBC.

acknowledgements

The authors take full responsibility for the content of this publication and confirm that it reflects their viewpoint and medical expertise. They also wish to acknowledge StemScientific, funded by Bristol-Myers Squibb, for providing writing and editing support. Neither Bristol-Myers Squibb nor StemScientific influenced the content of the manuscript, nor did the authors receive financial compensation for authoring the manuscript.

disclosure

The authors declare no conflict of interest.

references


