Achievements in Systemic Therapies in the Pregenomic Era in Metastatic Breast Cancer

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Key Words. Metastatic breast cancer  Chemotherapy  Endocrine therapy  Trastuzumab  Taxanes

LEARNING OBJECTIVES
After completing this course, the reader will be able to:

1. Identify the available systemic therapies for metastatic breast cancer patients.
2. Define the role of taxanes and targeted therapies in metastatic breast cancer patients.
3. Discuss the most useful endocrine therapy in patients with metastatic breast cancer.

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ABSTRACT
Over the last decades, the introduction of several new agents into clinical practice has significantly improved disease control and obtained some, albeit rare, survival benefits in metastatic breast cancer (MBC). Despite these results, the choice of treatment for the majority of patients is still empirically based, since the only two predictive factors with level 1 evidence for clinical use are hormonal receptor status for endocrine therapy and HER-2 status for trastuzumab therapy.

Important improvements in the endocrine therapy of both pre- and postmenopausal women with hormone-responsive disease have been achieved. For premenopausal women, ovarian function suppression with luteinizing hormone-releasing hormone analogs combined with tamoxifen has become the standard treatment, although aromatase inhibitors plus ovarian function suppression are under evaluation. In postmenopausal patients, aromatase inhibitors have proved to be superior to standard endocrine therapies in either first- or second-line treatment and a novel antiestrogen compound, fulvestrant, has been introduced in clinical practice.

Chemotherapy remains the treatment of choice for hormone unresponsive or resistant patients. Anthracyclines and taxanes have been used either alone or in combination as first-line chemotherapy, but with the more frequent use of these agents in the adjuvant setting, new standards are needed for first-line chemotherapy, and new and more efficacious treatments are required.

In the subgroup of patients with tumors that overexpress HER-2, the use of trastuzumab alone or in combination with chemotherapy has modified the natural history of these tumors, even if only about one out of two patients obtains a clinical response.

In this review we summarize the main achievements and the currently available treatment options for patients with MBC. The Oncologist 2007;12:253–270

Disclosure of potential conflicts of interest is found at the end of this article.
INTRODUCTION
Clinical research in the pregenomic era has achieved important advances in breast cancer (BC) treatment using empirical methods to compare different therapies. The only accepted predictive factors are hormonal receptor (HR) status to select endocrine therapy (ET) and, more recently, human epidermal growth factor receptor-2 (HER-2) status for the use of trastuzumab [1]. In spite of adequate primary therapy, many patients with apparently localized disease harbor subclinical micrometastases that may grow into clinically relevant macrometastases later on. In addition, 6%–10% of newly diagnosed BC patients have locally advanced or metastatic disease. Metastatic breast cancer (MBC) patients have a median survival period of 2–3 years [2], with few of them (2%) surviving 20 years after the diagnosis of metastasis [3]. This occurs despite the discovery of and incorporation into clinical practice of numerous new agents (e.g., taxanes, vinorelbine, capcitabine, gemcitabine, trastuzumab, aromatase inhibitors [AIs], and bisphosphonates) that can palliate the disease [4] and, more rarely, increase overall survival (OS) [5–12]. Therefore, for the majority of patients with MBC, “cure” is not the goal of treatment; instead, more conservative treatments are preferred to obtain maximum control of symptoms, prevent serious complications, and prolong life with minimal toxicities and disruption of quality of life (QoL).

Following the assessment of the extent of the disease, patients can be classified as “low risk” and “moderate/high risk,” according to the parameters shown in Table 1.

The observation that a higher objective response rate (ORR) and longer time to treatment progression (TTP) do not always translate into detectable OS advantages might be related to several factors: the pattern of BC growth, the small size of the majority of trials [13], and the study designs incorporating a crossover to the investigational drug or regimen. The most important advances and the new standards of care for endocrine, cytotoxic, and biological therapies in the era of “empirical oncology” are summarized in this review.

Endocrine Therapy
Since the observation made by Sir Beatson [14] more than 100 years ago that oophorectomy in premenopausal women could induce tumor regression, ET has been extensively used in the treatment of BC in all stages. The suppression of tumor growth can be obtained by: (a) reducing estrogen (E) levels with surgical, radiation, or chemical ovarian ablation (OA) in premenopausal women, or with AIs in postmenopausal women; (b) blocking the interaction between E and the estrogen receptor (ER) with selective ER modulators (SERMs); or (c) destroying the ER with selective ER down-regulators (SERDs). In MBC patients, the presence of HRs [15, 16] and their quantitative levels [16, 17] are strongly predictive of hormone responsiveness [18, 19]. However, about 30% of patients do not respond to ET even if both HRs (ER and the progesterone receptor [PgR]) are positive (de novo resistance), and a considerable percentage of initially responsive patients become resistant to it (acquired resistance).

Postmenopausal Patients
Tamoxifen, a nonsteroidal antiestrogen with partial agonist activity, began to be used in clinical trials for MBC in 1971 and has remained “the gold standard” for first-line ET for almost 30 years. The second-line drugs were mainly progestins and the first-generation AIs, aminoglutethimide (AG) with corticosteroid support. Recently, new hormonal agents have been developed, particularly novel AIs and antiestrogens.

AIs
Second-Line
The second- and third-generation AIs are more selective, better tolerated, and more potent than AG. Third-generation AIs are classified into two types, based on their chemical structure and mechanism of action: nonsteroidal/reversible (anastrozole, letrozole, and vorozole) and steroidal/irreversible (exemestane). The first randomized trials using these agents were conducted in postmenopausal women who had progressed on tamoxifen or relapsed within 12 months after stopping the drug as adjuvant therapy, and all four agents were compared with megestrol acetate (MA). The results of these trials [20–25] are summarized in Table 2.

Vorozole, although as effective as MA and better tolerated, was discontinued from clinical development [26]. Letrozole and vorozole were also compared with AG (500 mg/day) with corticosteroid support in a similar patient population [27, 28], and the main outcomes are shown in Table 2. Based on the results of these studies, third-generation AIs became the standard second-line ET for postmenopausal women with HR-positive tumors.

Only one randomized open-label multicenter trial has directly compared two third-generation AIs in postmenopausal patients with MBC considered refractory to antiestrogens [29]. A higher ORR was obtained with letrozole than with anastrozole in HR-positive patients and in those...
with visceral or soft tissue metastasis, without significant differences in TTP, time to treatment failure (TTF), or OS. Unfortunately, this study was not double blind, was industry sponsored, and the HR status was unknown in 52% of patients. AIs have also been evaluated as third-line therapy, and a lack of cross-resistance between them has been reported [30, 31]; the best sequence is still unknown [32].

**First-Line**

Based on the positive results obtained in second-line ET, anastrozole, letrozole, and exemestane were compared with tamoxifen as first-line therapy in large, phase III, randomized, multicenter trials enrolling postmenopausal women with HR-positive or unknown MBC. Adjuvant tamoxifen had to be completed at least 6 months previously. Anastrozole was evaluated in two identically designed studies, one conducted in the U.S./Canada [33, 34] and the other in Europe and the rest of the world [35]. No significant difference in ORR was reported in either study, while a significantly longer median TTP was observed only in the first one [33], in which the percentage of patients with HR-positive tumors was higher. Similarly, a statistically significant longer TTP favoring anastrozole in HR-positive patients was obtained pooling the data of the two studies [36]. Letrozole was superior to tamoxifen in a double-blind, double-dummy, randomized trial in which a crossover at progressive disease (PD) was included in the design [37, 38]. A significantly longer TTP and TTF and higher ORR and clinical benefit (CB) rate in the letrozole arm were observed in the entire population and in different subgroups selected according to previous adjuvant treatment with tamoxifen, HR status (positive or unknown), and dominant metastatic site. A higher ORR and a significantly longer progression-free survival (PFS) duration with exemestane in comparison with tamoxifen were reported [39].

The most important findings of each trial [33–39] are reported in Figure 1. The AIs were well tolerated, with better toxicity profiles than with tamoxifen. Following the publication of these results, AIs became the new gold standard first-line ET in postmenopausal MBC patients.

A meta-analysis of 23 published randomized controlled trials comparing several generations of AIs with standard ET (tamoxifen or progestagens) in MBC has recently shown a survival benefit with third-generation AIs as first-line as well as second- and subsequent-line treatment [40].

### Novel Antiestrogens

Several novel antiestrogen compounds, with a lower agonist profile on breast and gynecologic tissues in comparison with tamoxifen, have been developed. There are two major groups of agents: (a) the SERMs, further divided into triphenylethlenes, of which the parent compound is tamox-
ifen, and benzothiophenes, with a “fixed ring” structure; and (b) the SERDs, also called “pure antiestrogens,” which can be either steroidal or nonsteroidal. Among the latter, fulvestrant has obtained the most interesting results. This pure antiestrogen has a peculiar mechanism of action, downregulating the ER and reducing the PgR content of the tumor.

**Second-Line**

Fulvestrant was compared with anastrozole in two randomized phase III trials enrolling postmenopausal patients with locally advanced BC or MBC who had progressed after receiving tamoxifen as adjuvant or first-line therapy. In a combined analysis of both studies [41], there was no statistically significant difference between the two arms for all clinical outcomes, and, for the first time, an antiestrogen showed activity in patients refractory to tamoxifen.

**First-Line**

In postmenopausal patients with untreated MBC and HR-positive or unknown tumors, fulvestrant and tamoxifen have been compared in a large, double-blind, randomized trial. No significant differences in outcomes have been reported, but the TTF was statistically shorter in the fulvestrant group (5.9 months versus 7.8 months, respectively; \( p = .026 \)) [42]. A higher incidence of hot flushes was observed in patients treated with tamoxifen. These results could partially be explained by the pharmacokinetics of fulvestrant, because a monthly injection of fulvestrant, 250 mg, may take 3–6 months to produce steady-state plasma levels [42].

In conclusion, four categories of postmenopausal patients can be considered when selecting the sequence of ET agents in MBC: (a) ET naïve; (b) tamoxifen sensitive, if there was prior tamoxifen exposure but interval to the appearance of metastatic lesions was >1 year; (c) tamoxifen resistant, if there was prior tamoxifen exposure but the interval to relapse was ≤1 year; and (d) progressive on nonsteroidal AIs [43]. The first two categories can be viewed as one group in terms of therapy options, and for these patients the nonsteroidal or steroidal AIs are the first choice. For patients defined as tamoxifen resistant without previous exposure to AIs, these drugs or fulvestrant can be selected. In patients progressing on nonsteroidal AIs, the best hormonal agent—tamoxifen, fulvestrant, or exemestane—has not yet been defined. Indeed, a combined analysis of two international, randomized, double-blind trials has shown that 48% of patients showed a CB with tamoxifen administered after first-line anastrozole [44], although the opposite sequence was shown to be superior in a small, randomized, double-blind first-line crossover trial [45]. In phase II trials, fulvestrant after an AI or an AI and tamoxifen has been shown to have efficacy with an acceptable toxicity profile [46–48]. It is hoped that a better understanding of the mechanisms of resistance to antiestrogens and to AIs and how to prevent or delay resistance, together with the possibility of defining the subgroups of patients responsive to specific agents, will help us to select the best treatment approach for individual patients.

**PREMENOPAUSAL PATIENTS**

For premenopausal patients, endocrine options include oophorectomy, ovarian irradiation, or the use of luteinizing hormone-releasing hormone (LHRH) analogs, tamoxifen, or a combination of both. Surgical or radiation OA produced an ORR ranging from 30% in unselected patients [49, 50] to 79% in those with ER-positive tumors [51, 52]; comparative studies have shown similar results with the two procedures [53]. In the late 1970s and early 1980s, it was demonstrated that tamoxifen was also active in premenopausal women [54]. In three small trials [50, 55, 56] and in a meta-analysis of these studies [57], tamoxifen was as effective as OA as first-line treatment for ER-positive MBC. In a limited number of patients, both treatments were effective as second-line therapy at progression, but a significantly higher ORR occurred with OA. By the late 1980s and early 1990s, tamoxifen became the standard ET for premenopausal women with MBC, followed at progression by surgical or radiation OA and, subsequently, by the other hormonal agents used for postmenopausal women. In the early 1990s, however, LHRH analogs became available, and these agents are able to produce medical OA in premenopausal women, potentially reversible upon discontinuation of therapy. The tolerance profile of these drugs is good, and the most common side effects are hot flushes and tumor flare reactions. The largest phase III trial comparing
surgical OA with goserelin did not find differences in PFS, OS, or the ORR in 136 premenopausal patients with HR-positive MBC [58]. A combination of an LHRH analog and tamoxifen to obtain “complete estrogen blockade” was compared with an LHRH analog alone in three small, randomized studies in pre- and perimenopausal patients with ER-positive or unknown MBC [59–61]. A meta-analysis of these trials evaluating 506 patients showed a higher ORR, longer PFS time, and longer OS time in women treated with complete estrogen blockade. There are, however, some caveats about these data: (a) the number of patients enrolled in each study was small; (b) the ER positivity of tumors was confirmed in only 62% of patients; (c) the patients received various previous adjuvant treatments; (d) in three trials there was no formal crossover to tamoxifen as second-line therapy in patients treated with an LHRH analog alone; (e) the toxicity profile was not well reported; and (f) QoL evaluation was lacking. Nonetheless, the combination of an LHRH analog and tamoxifen is now accepted as the treatment of choice in premenopausal patients with MBC. A new promising option could be the combination of an LHRH analog and an AI, but, presently, few data are available [62–66].

CHEMOTHERAPY
Chemotherapy (CT) is currently the only therapeutic option for women with HER-2-negative, endocrine-resistant MBC, or for women with extensive visceral localizations or life-threatening disease. The most used drugs are anthracyclines, taxanes, alkylating agents, antimetabolites, and vinca-alkaloids. Used as single agents, they produce an ORR of 20%–80% [67–69], whereas the combinations seem to increase the ORR but not the percentage of complete responses (CRs). Furthermore, the majority of CRs are short lived [3, 70]. An interesting correlation between CR and long-term disease-free survival has been reported in studies using both standard-dose and high-dose CT [3, 71, 72]. According to these studies, it appears that a CR is necessary but not sufficient to predict long-term PFS; however, other authors consider CR a valid surrogate endpoint for OS [73].

Pre-Taxane Era
In the pre-taxane era, several combination regimens were developed, and these yielded higher ORRs, sometimes longer TTP, and even longer OS times in comparison with monochemotherapies [74–83]. In a meta-analysis of randomized trials, anthracycline-containing regimens were found to be superior to a combination of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) [13]. Furthermore, no significant differences were observed between doxorubicin and epirubicin at equivalent doses, but epirubicin was less toxic in a meta-analysis of comparative randomized trials [84].

Taxane Era

Anthracycline-Naïve or Minimally Exposed Patients

Taxanes as Monochemotherapy. Paclitaxel and docetaxel have both been compared with doxorubicin in the first-line treatment of MBC. In one study, docetaxel produced a higher ORR than doxorubicin, but no difference in TTP or OS time [85]; in a three-arm study, paclitaxel was compared with doxorubicin and with the combination of the two drugs, with no statistically significant differences between the two single agents, although a higher ORR and longer TTP was shown for the combination [86]. In another study, doxorubicin was superior to paclitaxel in terms of ORR and TTP [87]. A significantly longer OS time after adjustment for prognostic factors, without differences in the ORR and TTP, was obtained with paclitaxel in comparison with CMF plus prednisone in untreated patients [6], but this advantage could be attributed to a better sequence of treatments, because about 40% of the patients received anthracyclines at progression. The criticisms of most of these trials are summarized in Table 3, and their results can be found in Table 4.

Taxanes as Combination Therapy. Several studies have compared combinations of taxanes and anthracyclines with standard anthracycline-based regimens as first-line treatment for anthracycline-untreated or minimally exposed MBC patients. Paclitaxel plus doxorubicin yielded a significantly greater ORR, longer TTP, and longer OS time in comparison with a combination of fluorouracil, doxorubicin, and cyclophosphamide (FAC), but with a significantly higher incidence of grade 3 or 4 neutropenia. However, QoL was similar with the two regimens [10]. The weakness of this study is to be found in the suboptimal dose of the FAC regimen chosen and the fact that only one fourth of the patients treated with this regimen received anthracyclines at progression. No significant differences were observed in three other large trials comparing a combination of paclitaxel and doxorubicin [88] or paclitaxel and epirubicin [89, 90] with standard regimens containing doxorubicin/epirubicin and cyclophosphamide.

Docetaxel in combination with doxorubicin (AD) [91] or with doxorubicin and cyclophosphamide (TAC) [92] has been compared with standard regimens such as doxorubicin and cyclophosphamide (AC) or FAC. A higher ORR was observed in both trials, but only in one
[91] did this translate into a longer TTP. A significantly higher incidence of grade 3 or 4 hematological and non-hematological toxicities was reported with the TAC regimen, including more cardiotoxicity. Similar results, with a significantly longer OS time but higher incidence of febrile neutropenia and two toxic deaths in the docetaxel arm, were reported in a trial comparing AD with FAC as first-line CT in MBC patients [12]. The lack of minimal crossover reports in the taxane trials does not enable a definite conclusion to be drawn regarding the value of combination CT versus the sequential use of single agents. These studies are summarized in Table 5. An additional trial that compared a combination of docetaxel or paclitaxel with doxorubicin as first-line metastatic CT did not show any significant difference in ORR, PFS, or OS between the two arms [93]. Furthermore, in a recent meta-analysis of taxanes alone or in combination with anthracyclines as first-line CT for MBC, single-agent anthracycline therapy was significantly better than single-agent taxane therapy in terms of PFS, but not in terms of

Table 3. Overview of randomized phase III trials of taxanes in metastatic breast cancer patients with minimal or no previous anthracycline exposure and after anthracycline failure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>RR (p-value)</th>
<th>RR at crossover (%)</th>
<th>TTP (p-value)</th>
<th>OS (months) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>47.8% (.008)</td>
<td>No</td>
<td>26 weeks</td>
<td>15</td>
</tr>
<tr>
<td>Doxorubicin [85]</td>
<td>33.3%</td>
<td></td>
<td>21 weeks</td>
<td>14</td>
</tr>
<tr>
<td>Paclitaxel/doxorubicin [86]</td>
<td>47% (.007)</td>
<td></td>
<td>8.2 months</td>
<td>22.4</td>
</tr>
<tr>
<td>Paclitaxel [87]</td>
<td>25% (.003)</td>
<td>16%</td>
<td>3.9 monthsb</td>
<td>15.6</td>
</tr>
<tr>
<td>Doxorubicin [87]</td>
<td>41%</td>
<td>30%</td>
<td>7.5 months</td>
<td>18.3 (.38)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>29% (.37)</td>
<td>No</td>
<td>5.3 months</td>
<td>17.3 (.068)</td>
</tr>
</tbody>
</table>

Abbreviations: C, cyclophosphamide; F, 5-fluorouracil; M, methotrexate; NS, not significant; OS, overall survival; p, prednisone; RR, response rate; TTP, time to progression.

Table 4. Randomized trials of single-agent taxanes in metastatic breast cancer patients with minimal or no previous anthracycline exposure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n of patients</th>
<th>RR (p-value)</th>
<th>RR at crossover (%)</th>
<th>TTP (p-value)</th>
<th>OS (months) (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Docetaxel</td>
<td>326</td>
<td>47.8% (.008)</td>
<td>No</td>
<td>26 weeks</td>
<td>15</td>
</tr>
<tr>
<td>Doxorubicin [85]</td>
<td>36%</td>
<td></td>
<td>21 weeks</td>
<td>14</td>
<td></td>
</tr>
<tr>
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<td>47% (.007)</td>
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<td>(.38)</td>
</tr>
<tr>
<td>Paclitaxel</td>
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<td>No</td>
<td>5.3 months</td>
<td>17.3</td>
<td>(.068)</td>
</tr>
</tbody>
</table>

Abbreviations: ORR, overall response rate; OS, overall survival; TTP, time to progression.

[8]Progression-free survival.
OS; taxanes in combinations, moreover, resulted in a significantly better ORR than with anthracycline-containing combinations, but were only marginally better in terms of PFS and not in terms of OS [94].

**Anthracycline Resistant or Refractory Patients**

The common use of anthracycline-based regimens in the adjuvant setting has increased the likelihood of anthracycline-resistant MBC. In phase II trials, docetaxel as a single agent has produced a high ORR [95, 96] and, compared with non–anthracyclines-based regimens in a similar patient population, has shown a higher ORR with a significantly longer TTP in one trial [97], and also a significantly longer OS time in another one [7]. Although crossover had not been planned in those studies, docetaxel can be considered the standard of care as monotherapy for anthracycline resistant or refractory patients, particularly because there are no studies with paclitaxel as monotherapy.

Taxane-based combinations without anthracyclines have also been evaluated in this population. In a phase III randomized multicenter trial, a combination of docetaxel plus capecitabine was compared with single-agent docetaxel [9]. The combination achieved a higher ORR and longer median TTP, and also a significantly longer OS time of 3 months. QoL was similar, while toxicities in the two treatment arms were different. Neutropenic fever/sepsis, myalgia, and arthralgia were more common in the docetaxel arm, whilst gastrointestinal side effects and hand-foot syndrome occurred more frequently in the combination arm. An interesting aspect of this study relates to the preclinical evidence of synergy between docetaxel and capecitabine [98, 99], even if the nature of this interaction has yet to be fully defined. In another large trial with a similar design, three-weekly paclitaxel was compared with a combination of gemcitabine and paclitaxel that yielded superior results in terms of ORR, TTP [100], and OS [101]. The lack of a planned crossover does not allow for a comparison between the combination and the sequential approach in these two trials; however, the U.S. Food and Drug Administration (FDA) has approved both combination regimens for the first-line treatment of MBC patients pretreated with anthracyclines [102]. In anthracycline-pretreated MBC pa-

### Table 5. Randomized trials of anthracycline/taxane combinations versus polychemotherapy in metastatic breast cancer patients with minimal or no previous anthracycline exposure

<table>
<thead>
<tr>
<th>Regimen</th>
<th>n of patients</th>
<th>RR (p-value)</th>
<th>RR at crossover (%)</th>
<th>TTP (p-value)</th>
<th>OS (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Docetaxel-based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AD AC [91]</td>
<td>429</td>
<td>59% (0.09)</td>
<td>No</td>
<td>37.3 weeks (0.014)</td>
<td>22.5 weeks (0.26)</td>
</tr>
<tr>
<td>DAC FAC [92]</td>
<td>484</td>
<td>55% (0.023)</td>
<td>No</td>
<td>31 weeks (0.51)</td>
<td>21 months (0.93)</td>
</tr>
<tr>
<td>AD FAC [12]</td>
<td>216</td>
<td>58% (0.003)</td>
<td>No</td>
<td>8.0 months (0.004)</td>
<td>22.6 months (0.019)</td>
</tr>
<tr>
<td><strong>Paclitaxel-based</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AP FAC [10]</td>
<td>267</td>
<td>68% (0.032)</td>
<td>No</td>
<td>8.3 months (0.034)</td>
<td>23.3 months (0.013)</td>
</tr>
<tr>
<td>AP AC [88]</td>
<td>275</td>
<td>58% (0.51)</td>
<td>No</td>
<td>6.0 months (0.65)</td>
<td>20.6 months (0.49)</td>
</tr>
<tr>
<td>EP EC [90]</td>
<td>705</td>
<td>65% (0.015)</td>
<td>No</td>
<td>7.0 months (0.41)</td>
<td>13 months (0.8)</td>
</tr>
<tr>
<td>EP EC [89]</td>
<td>560</td>
<td>46% (0.89)</td>
<td>No</td>
<td>39 weeks (0.33 weeks)</td>
<td>NR</td>
</tr>
</tbody>
</table>

*The primary endpoint was progression-free survival.

Abbreviations: A, doxorubicin; D, docetaxel; E, epirubicin; F, 5-fluorouracil; C, cyclophosphamide; P, paclitaxel; NR, not reported; OS, overall survival; RR, response rate; TTP, time to progression.
tients, no differences in ORR, duration of response, median TTF, or PFS were observed in a phase III trial comparing docetaxel plus gemcitabine with docetaxel plus capecitabine. However, treatment discontinuation due to adverse events was more frequently reported in the capecitabine combination arm (28% versus 13%; \( p = .014 \)), which could be related to the quite high doses used for both drugs [103].

Another phase III trial comparing docetaxel with vinorelbine plus 5-fluorouracil in 86 anthracycline-refractory patients failed to show any difference in TTP or OS, but docetaxel was less toxic, except for neutropenia [104].

ABI-007 (Abraxane®; AstraZeneca, Wilmington, DE) is a novel, biologically interactive, albumin-bound paclitaxel in a nanometer particle, free of solvents, developed to avoid toxicities associated with polyethylated castor oil. The drug was compared with standard paclitaxel in patients with MBC, candidates for single-agent paclitaxel in a phase III study. About 50% of patients had previously received anthracycline-based therapy for metastatic disease. ABI-007 was associated with a significantly higher response rate compared with standard paclitaxel (33% versus 19%; \( p = .001 \)) and longer TTP (23.0 versus 16.9 weeks; hazard ratio = 0.75; \( p = .006 \)). Interestingly, a significantly longer OS time was observed in the subgroup of patients who received ABI-007, compared with standard paclitaxel, as second-line or greater therapy (56.4 versus 46.7 weeks; \( p = .024 \)). The incidence of grade 4 neutropenia was significantly lower for ABI-007 (9% versus 22%; \( p < .001 \)), despite a 49% higher paclitaxel dose; however, grade 3 sensory neuropathy was more common in the ABI-007 arm (10% versus 2%; \( p < .001 \)), albeit easily managed and rapidly improving (median 22 days). No hypersensitivity reactions occurred with ABI-007 despite the absence of premedication and shorter administration time [105].

**Which Taxane and Which Dose?**

In the TAX-311 study, docetaxel and paclitaxel, both administered every 3 weeks in MBC patients resistant to anthracyclines, were compared head to head [111]. In this industry-sponsored trial, the median TTP and OS time were significantly longer in the docetaxel arm, but the ORR, although higher, did not reach statistical significance. These advantages were, however, associated with greater hematological and nonhematological toxicities and with four treatment-related deaths.

Both taxanes can be administered every 3 weeks and weekly. For paclitaxel, several prospective studies have compared different doses and different infusion times, but none has so far shown a clear advantage over the registered one (175 mg/m² as a 3-hour infusion) given every 3 weeks [106–109]. General consensus exists for the dose and infusion time of docetaxel (100 mg/m² in 1 hour) approved for the treatment of MBC in the U.S. and in Europe. Recently, three different doses of docetaxel (60, 75, and 100 mg/m²) have been evaluated in pretreated MBC patients [110], and although significantly higher ORRs were obtained with high doses, no difference in median TTP and OS among the three arms was reported in the intention-to-treat analysis. Most hematologic and nonhematologic toxicities were related to increasing doses, with grade 3–4 neutropenia and febrile neutropenia occurring in a higher percentage of patients with the highest dose.

The weekly administration of taxanes has received growing interest as a way to increase efficacy and/or decrease toxicity. The only advantage reported for weekly docetaxel has been a reduction in myelosuppression. In contrast, the mechanism of action of weekly paclitaxel seems different [111], and recently, in a phase III randomized trial comparing weekly with every-3-week paclitaxel with and without trastuzumab in HER-2-negative or overexpressing MBC patients, a higher ORR and longer TTP were reported with the weekly schedule [112].

Of note, preclinical and clinical data have shown that crossresistance between the two taxanes is only partial; consequently, their sequential use a few months apart is possible, in particular for initially responsive patients [113, 114].

**Anthracycline- and Taxane-Resistant Patients**

No standard of care exists after failure of both anthracycline and taxane treatment, and options for patients in this situation are limited. The most common treatments are chosen in view of their manageable toxicity profiles and reasonable efficacy, because no randomized study has so far demonstrated a benefit in OS after second-line CT [70].

Capecitabine is the first oral fluoropyrimidine approved by the FDA for the treatment of MBC patients whose prior anthracycline- and taxane-based CT has failed. At least five phase II trials enrolling 547 anthracycline- and/or taxane-pretreated patients have been reported. Capecitabine as a single agent produced an ORR of 15%–29% and a median OS duration of 9.4–15.2 months [115–119]. The drug alone or in combination has also been evaluated in anthracycline-pretreated and untreated MBC patients in phase II trials [120–123].

Intravenous vinorelbine has shown a variable ORR (10%–20%) after anthracycline or taxane failure [124, 125], with a low incidence of nonhematological toxicities. An oral formulation of vinorelbine has been evaluated recently as first-line chemotherapy for MBC, and the results suggest that it is an effective and well-tolerated agent, offering an alternative to the i.v. route [126]. Vinorelbine also
performed better than oxaliplatin in PFS and OS in a phase III trial [127]. Irinotecan given either weekly or every 3 weeks showed some response in this subset of patients [128]. More recently, epothilones, a new class of antitubulin agents that lacks crossresistance with the taxanes, have been developed in the metastatic setting, with promising results [129, 130].

Pegylated liposomal doxorubicin has also been tested in MBC with encouraging results and less cardiotoxicity. In a randomized phase III trial, pegylated liposomal doxorubicin HCL (Caelyx®; Schering-Plough Corporation, Kenilworth, NJ) showed similar results in terms of ORR, PFS, and OS when compared with doxorubicin as first-line CT, with significantly lower cardiotoxicity but a higher incidence of palmar–plantar erythrodysesthesia [131]. Similar results were seen with nonpegylated liposomal doxorubicin (Myocet®; Sopherion Therapeutics, Inc., Princeton, NJ) in comparison with doxorubicin as a single agent or in combination with cyclophosphamide [132, 133]. However, in a randomized phase III trial in taxane-refractory MBC patients, pegylated liposomal doxorubicin yielded a significantly longer PFS time than the comparator (vinorelbine or mitomycin plus vinblastine) in the subgroup of anthracycline-naïve patients [134].

**Combination Versus Sequential CT**

The question of “optimal” modality of administering antitumor agents, sequentially or in combination, remains controversial, and it is doubtful that either strategy is appropriate for all patients.

The ideal combination regimen should include active and non-crossresistant single agents with preclinical evidence of synergy and nonoverlapping side effects. However, all three criteria are rarely met and, consequently, several combination therapies have failed to result in significantly longer OS when compared with single agents administered sequentially both in the pre-taxane [135, 136] and in the taxane era [86, 137–139].

Sequential administration of CT allows us to give each drug at its maximum tolerated dose, avoiding overlapping toxic effects. It is possible to introduce a new drug following disease progression or plan multicourse sequences of CT agents without a break between the different drugs.

In a phase III trial, a combination of doxorubicin and paclitaxel in comparison with the sequential administration of each drug at progression (paclitaxel followed by doxorubicin or vice versa) resulted in a statistically significant higher ORR and longer TTP without differences in OS. The QoL was similar in the three arms, even if grade 3 and 4 toxicities were inferior with the sequential schedules [86].

In two other trials using a combination of capecitabine and taxanes with a similar design but differences in type of trial, doses and order of sequence of the two drugs, and taxane used [140, 141], a higher ORR was reported, but this translated into a longer TTP and OS only in one trial [141].

Two phase II trials [142, 143] and three phase II randomized trials [137–139] have compared combination chemotherapy with planned sequential therapy, with no significant differences in activity and efficacy but a better safety profile with sequential therapy in the majority of trials.

Further indirect support to the sequential use of cytotoxic drugs can be derived from the results of other trials showing that single agents were superior to combinations because of better tolerance and similar efficacy [144, 145], or better clinical outcome [6, 7]. Therefore, individualized treatment is preferable and should be based on several factors, such as tumor-associated symptoms, extent of visceral disease, comorbidities, age, and performance status. In any case, life expectancy in this setting is relatively short, and a gain of a few months must be balanced with treatment-related toxicity, patient QoL, and patient preference.

At present, in the absence of specific predictive factors to prospectively select a subgroup of responsive patients, combination CT should be reserved for patients with rapidly progressing visceral metastatic disease, or in emergency situations in which a rapid response is warranted.

**Duration of CT**

The optimal duration of CT administration in the absence of PD is not well defined. A meta-analysis [146] of three trials comparing a shorter with a longer duration of the same CT in women with MBC [147–149] indicated a statistically significant but modest survival advantage for those randomized to the longer duration. These data were confirmed by a fourth trial published shortly thereafter [150]. Small increments in survival duration have a high value for women with MBC [151]; however, these advantages must be weighed against the additional subjective toxicity of continued CT. QoL was measured in only one of these trials [147], and was better in patients receiving longer CT. In contrast, longer therapy resulted in no significant differences in OS and in a slight reduction in mean quality-adjusted survival time in another randomized trial conducted by the European Organization for Research and Treatment of Cancer Breast Cancer Group [152]. A significantly longer TTF was reported in patients continuing the treatment, but this was <2 months. It should be noted that all these studies were conducted in the pre-taxane era. Because the tolerability of these “new” drugs is different from previously used ones, as well as dose limiting, other strategies are being evaluated or need to be investigated in an attempt to maintain response or stabilization of disease.

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Examples include metronomic therapies, biological agents, and ET in patients with HR-positive tumors.

**Biological Therapies**

With the growing understanding of the biology of BC and the advent of new techniques, such as genomics and proteomics, multiple new targets for anticancer therapy have been identified. These molecules are implicated in several pathways relevant to the biology of the BC cell, such as the signal transduction pathway, the cell cycle, the apoptotic pathway, and the angiogenesis/metastasis pathway. To date, the only biological agent approved in Europe for the treatment of MBC is trastuzumab, a humanized monoclonal antibody directed against the external domain of HER-2.

**Trastuzumab**

The efficacy of trastuzumab is highly dependent on the HER-2 status of the tumor, and its benefits are only observed in patients with HER-2–positive tumors, defined as a 3+ overexpression score by immunohistochemistry (IHC) or gene amplification by fluorescence in situ hybridization (FISH). In HER-2–positive pretreated MBC patients, single-agent trastuzumab yielded an ORR of 18% [153] that increased to 35% if it was used as first-line therapy [154]. In HER-2–positive untreated MBC patients, the addition of trastuzumab to CT resulted in a higher ORR and longer duration of response, TTP, and OS time in comparison with CT alone [8]. The longer OS time was particularly noteworthy, considering that approximately 66% of patients treated with CT alone had received trastuzumab at the time of PD. The combination of trastuzumab and taxanes, paclitaxel, and more recently docetaxel [155], is the one recommended; this is a result of the quite high incidence of cardiac dysfunction reported with the association of trastuzumab and anthracycline-based regimens.

Several other single agents have been successfully combined with trastuzumab in phase II trials and include weekly paclitaxel [156], weekly [157] or three-weekly [158] docetaxel, vinorelbine [159–161], gemcitabine [162, 163], capecitabine [164, 165], liposomal doxorubicin [166, 167], and cisplatin [168]. Combinations of two cytotoxic agents and trastuzumab are also being evaluated and, so far, better results have been reported in randomized trials with the association of paclitaxel/carboplatin and trastuzumab [169] or platinum salts/docetaxel and trastuzumab [170], in comparison with regimens with a taxane and trastuzumab.

Despite the impressive results obtained with trastuzumab, about 50% of patients with HER-2–positive MBC will not benefit from this agent, and the median duration of response is between 9 and 12 months. Therefore, both de novo and acquired resistance to trastuzumab occurs, and other factors, besides HER-2 expression, must be involved in the response to this agent [171].

HER-2 overexpression has been associated with preclinical and clinical resistance to ET, particularly tamoxifen [172–175]. A meta-analysis based on 12 studies and 2,379 patients showed a high correlation between retrospectively assessed HER-2 overexpression and ET failure (tamoxifen or other agents) that was even higher when the few ER-negative patients were excluded [175]. Controversial results have been reported with AIs [176–178]. Significant preclinical evidence suggests that intensive crosstalk between HER-2 and ER occurs in BC cells and there is a rationale to combine trastuzumab with antiestrogens [179]; this is being evaluated in an ongoing clinical trial. Even though the data regarding the importance of the interactions between the two pathways in patients treated with AIs are less clear, several trials are examining the potential of combining trastuzumab with these agents.

The most common schedule of administration of trastuzumab is a weekly i.v. infusion; however, because this drug has a long half-life of approximately 28 days, an alternate 3-weekly dosing regimen has been studied as monotherapy [180] or in combination with 3-weekly paclitaxel [181]. Further refinements to the trastuzumab schedule of administration are currently under evaluation, specifically with respect to the impact of a loading dose. Trastuzumab is commonly administered until PD, because a significant CB has been demonstrated in clinical trials with such designs. However, preclinical data and retrospective studies suggest a rationale for using trastuzumab beyond PD in combination with different cytotoxic agents [92, 182, 183]. Two randomized phase III trials are ongoing to try to prove this hypothesis: the MD Anderson Cancer Center trial with vinorelbine and a German study with capecitabine. In particular, when the central nervous system (CNS) is the only site of progression and systemic disease is otherwise well controlled, it seems logical to continue trastuzumab while appropriately managing the CNS metastasis.

Trastuzumab is quite well tolerated, with the exception of hypersensitivity reactions seen mainly with the first infusion. The only worrying side effect is the development of cardiac dysfunction [184] reported in about 4% of patients when trastuzumab is used alone, but increasing to 13% if combined with paclitaxel, and to 27% with anthracyclines. Trastuzumab-induced congestive heart failure is usually successfully treated with standard treatment and is not dose dependent, and the recovery from symptoms occurs even if the drug is continued [185, 186]. Age >60 and the association with a “classic” anthracycline were the only statistically significant predictive factors of cardiac toxicity.

There are still several undefined issues regarding the
clinical use of trastuzumab. These include (a) the optimal method and timing for HER-2 status assessment; (b) the optimal schedule of trastuzumab administration, dose, and duration; (c) the mechanism of cardiotoxicity; and (d) the emergence of resistance. Based on the available data, the key messages for the treatment of HER-2–positive MBC are: (a) early use of trastuzumab alone or in combination with cytotoxic agents, according to patient and tumor characteristics and previous treatments; (b) careful cardiac monitoring of left ventricular ejection fraction by multi-gated acquisition (MUGA) scanning or echocardiography, currently recommended every 3 months [187]; (c) special attention to CNS symptoms/signs, because of the propensity for brain metastasis in these patients, even with a stable or responding peripheral tumor burden [188–190].

With the increasing use of trastuzumab in the adjuvant setting, we are facing now a new issue—the treatment of patients who relapse while receiving or after treatment with trastuzumab. For these patients, it is possible to restart treatment with trastuzumab plus CT, but new drugs to overcome this resistance are needed.

Lapatinib

Lapatinib is an oral, selective and highly potent dual competitive inhibitor of HER-1 and HER-2 tyrosine kinases [191]. Recently, a phase III trial evaluated the administration of capecitabine with or without lapatinib in the treatment of 321 patients with HER-2–positive locally advanced BC or MBC refractory to trastuzumab (study EGF 100151). The median TTP in the combination arm (oral lapatinib, 1,250 mg, plus capecitabine, 2,000 mg/m²/d on days 1–14 every 3 weeks) was higher than that in the capecitabine alone (2,500 mg/m²/d on days 1–14 every 3 weeks) arm (36.9 weeks versus 19.7 weeks; \( p < .001; \) HR = 0.51, CI = 0.35–0.74) without major increases in toxicity [192]. Also noteworthy is the modest but clear activity of lapatinib against brain metastasis, shown in 38 heavily pretreated women with CNS progression or relapse, all previously exposed to trastuzumab (5.1% RR). In addition, eight patients showed CNS stabilization at 8 weeks and four at 24 weeks of treatment [193].

The main toxicities observed with lapatinib are diarrhea, skin rash, nausea, and fatigue. An ongoing randomized trial is evaluating the activity of lapatinib alone or in combination with weekly trastuzumab in patients refractory to trastuzumab.

This agent is the most advanced in terms of clinical development and has a favorable safety profile. Its promising activity in advanced breast cancer makes it the ideal candidate for testing in the adjuvant setting. Accordingly, the Breast International Group will soon launch two important trials evaluating lapatinib in the neoadjuvant (450 patients) and adjuvant (8,000 patients) settings.

Bevacizumab

Tumor growth depends upon angiogenesis, and cancer cells begin to promote this process early in tumorigenesis. This angiogenic impulse is characterized by oncogene-driven tumor expression of proangiogenic proteins, including vascular endothelial growth factor (VEGF). VEGF is an attractive target for antiangiogenic therapy because its receptors are present almost exclusively on genetically stable, non-neoplastic endothelial cells, and are upregulated in tumor vessels when compared with normal endothelium.

Bevacizumab (recombinant humanized monoclonal antibody [rHumAb]-VEGF) is a recombinant, humanized monoclonal antibody directed against VEGF. In a randomized phase III trial, bevacizumab combined with capecitabine produced a significantly greater ORR in comparison with capecitabine alone, but had no impact on PFS or OS in pretreated MBC patients [194]. Conversely, interesting results have recently been reported in untreated MBC patients with bevacizumab combined with weekly paclitaxel (ECOG 2100) [195]. This combination has produced a significantly greater ORR and longer PFS time in comparison with weekly paclitaxel alone. As expected, higher incidences of hypertension requiring treatment, bleeding, grade 3 or 4 proteinuria, and neuropathy were observed in the bevacizumab arm. A statistically nonsignificant advantage in OS has also been observed even though the median OS time has just been reached. One criticism of this study is related to the low ORR observed in the control arm, which could be a result of the weekly schedule used, the dose selected, or patient selection.

Therefore, although very intriguing, these data need to be confirmed in other randomized trials. The different results observed in these two bevacizumab trials might be explained by the important differences in patient population. In the ECOG 2100 trial, all patients received the combination as first-line therapy for MBC, while in the capecitabine/bevacizumab trial, 84.9% of patients had previously received CT for MBC, mostly anthracyclines and taxanes. This could suggest that antiangiogenic agents should be given early in the course of disease.

An additional problem surrounding bevacizumab is the lack of valid predictive factors that can help to select patients most likely to benefit from this agent. Additionally, some studies have failed to show any predictive value of urine VEGF and vascular cell adhesion molecule (VCAM)-1 [195]. For this reason, some experts refer to bevacizumab as “a targeted therapy without a target.”
CONCLUSIONS AND FUTURE PERSPECTIVES

The achievements obtained in MBC treatment in the so-called pregenomic era have been impressive and have led to longer PFS and OS times. The median survival time in patients with MBC has increased significantly in the last decade from 438 days during the years 1991–1992 to 667 days in 1999–2001 [196]. Randomized trials have been fundamental in helping us to select our treatment strategies, but the aim of MBC therapy is still essentially palliative and focused on improving QoL.

Tamoxifen, the gold standard ET for decades, has been replaced by the third-generation AIs as first-line ET for the majority of postmenopausal patients with endocrine-responsive disease, but we still do not know the best strategy for subsequent lines of treatment. Furthermore, a better understanding of the mechanisms of resistance to endocrine agents is necessary. For patients with endocrine nonresponsive disease, the use of anthracyclines and taxanes has changed the way we treat metastatic patients, but with their wider use in the adjuvant setting new standards of care are needed. Several drugs have shown activity after the failure of these agents, such as capecitabine, vinorelbine, and gemcitabine, but new drugs with different mechanisms of action and new combinations are eagerly awaited.

HER-2–positive BC should be considered a separate entity and treated accordingly. The use of trastuzumab in patients with HER-2–overexpressing tumors has changed the natural history of this disease and can probably be considered the most important achievement to date in the treatment of BC.

There are still many unanswered questions and new drugs are under evaluation.

The scarcity of agreement on standards of care renders the treatment of MBC complex. Furthermore, this disease requires a multidisciplinary team approach, with the early involvement of psychosocial support and palliative interventions as part of routine patient care. Patients must be encouraged to be actively involved in the treatment decision-making process; and their enrolment in well-designed trials is highly recommended.

With the development of new technologies, namely genomics and proteomics, we are aware that BC is not just a single entity but a complex disease with considerable molecular diversity that often translates into different clinical phenotypes. A better definition of these subtypes will probably change our treatment approach, moving from the era of empirically based treatment to the era of tailored therapies for each individual patient.

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DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

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