Treating Metastatic Breast Cancer With Systemic Chemotherapies: Current Trends and Future Perspectives

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Treatment selection for metastatic breast cancer (MBC) is guided by multiple factors, most importantly hormone receptor (HR) or HER2 expression, treatment history, and prognostic factors such as short disease-free interval, presence of visceral metastases, performance status, and degree of symptoms. Chemotherapy is indicated as initial therapy for patients with HR-negative disease and following failure of hormonal therapies in HR-positive disease. Patients treated with an anthracycline or a taxane in early-stage settings may no longer be candidates for those drugs in MBC, thus underscoring the need for alternative options. Sequential single-agent therapy or combination therapy are viable strategies. Trials have shown that ixabepilone plus capecitabine significantly improves progression-free survival compared with capecitabine alone in anthracycline- or taxane-pretreated or -resistant patients, and single-agent eribulin improves survival compared with the physician’s choice of treatment in patients treated previously with at least two regimens for MBC. Regardless of the regimen, proactive management to detect treatment-related adverse events in a timely manner remains important for ensuring effective delivery of treatment. Many promising investigational agents are in development, including T-DM1 (trastuzumab emtansine) and pertuzumab for HER2-positive disease, as well as PARP-1 (poly[adenosine diphosphate ribose] polymerase-1) inhibitors and cetuximab for triple-negative disease. In addition, new options for the treatment of MBC following failure of an anthracycline and a taxane promise to improve patient outcomes. Nurses should remain vigilant for adverse events and remember that the goal of treatment remains control of the disease and palliation.

Breast cancer is the most common malignancy and the second leading cause of cancer-related death among women in the United States, with an estimated 226,870 new cases diagnosed and 39,510 deaths occurring in 2012 (Siegel, Naishadham, & Jemal, 2012). About 5% of cases are diagnosed after the disease already has metastasized (Surveillance Epidemiology and End Results, 2012), and disease recurrence from early stage to distant sites is common. With the development of metastatic breast cancer (MBC), systemic treatment prolongs survival and enhances quality of life, but is not curative (National Comprehensive Cancer Network [NCCN], 2011). This article reviews current treatment strategies and trends in MBC and discusses several agents in clinical development. For all treatments discussed, nurses should remember that when patients fail to derive even a minor response from three sequential regimens or performance status is 3 or higher on a scale from 0–5 (higher scores indicate deteriorating performance), treatment should be changed to supportive care only (NCCN, 2011).

Current Treatment Options

The most important factors guiding the choice of initial therapy for MBC are hormone receptor (HR) and HER2 status, as well as prior treatments in early-stage disease (see Figure 1).

Hormonal Therapy

Hormonal therapy—either an aromatase inhibitor (anastrozole, letrozole, and exemestane) or an antiestrogen (tamoxifen)—
is used to treat postmenopausal women with tumors positive for estrogen receptor or progesterone receptor expression (NCCN, 2011). Aromatase inhibitors may offer a modest increase in overall survival (Bonneterre et al., 2000; Mouridsen et al., 2003) or progression-free survival (Paridaens et al., 2008) compared with tamoxifen in initial hormonal therapy of HR-positive MBC. The same hormonal therapy options are indicated for premenopausal women, but they generally are used in conjunction with ovarian ablation or suppression (Klijn et al., 2001; NCCN, 2011; Tan & Wolff, 2007). Women who respond or achieve long-term disease control on initial hormonal therapy may benefit from additional hormonal agents after disease progression (NCCN, 2011). For example, patients progressing on tamoxifen or aromatase inhibitor therapy may benefit from the antiestrogen fulvestrant (Di Leo et al., 2010; Ingle et al., 2006; Perey et al., 2007); those progressing on a nonsteroidal aromatase inhibitor may benefit from the steroidal aromatase inhibitor exemestane (Chia et al., 2008).

**Cytotoxic Chemotherapy**

Cytotoxic chemotherapy is the initial treatment for HR-negative MBC and for HR-positive disease with symptomatic visceral metastases or refractory to hormonal therapy (NCCN, 2011). Multiple classes of cytotoxic drugs are active in MBC, including anthracyclines (doxorubicin and epirubicin), taxanes (paclitaxel and docetaxel), nontaxane microtubule inhibitors (ixabepilone, vinorelbine, and eribulin), and antimetabolites (capecitabine and gemcitabine). The platinum-containing drugs (cisplatin and carboplatin) are receiving renewed interest for treating metastatic estrogen receptor–, progesterone receptor–, and HER2-negative breast cancer (triple negative).

The choice of cytotoxic chemotherapy is guided by treatment history. Anthracyclines or taxanes commonly are used in first-line MBC and produce comparable overall survival and response rates (Piccart-Gebhart et al., 2008). Those drugs frequently are used in early-stage disease; therefore, they may not be viable options once metastatic disease develops, particularly within 12 months of adjuvant or neoadjuvant therapy (Conte, Guarneri, & Bengala, 2007). Anthracyclines are limited by total cumulative dose because of cardiotoxicity, whereas taxanes (as well as anthracyclines) may lose effectiveness because of resistance mechanisms.

Additional lines of chemotherapy are indicated following disease progression on the first-line regimen. However, once patients fail to derive even a minor response from three sequential regimens or performance status deteriorates to 3 or higher (range = 0–5), treatment should be changed to supportive care only, as mentioned previously (NCCN, 2011).
Biologic Therapy

Biologic agents include the anti-HER2 monoclonal antibody trastuzumab, the dual HER2 and epidermal growth factor receptor tyrosine kinase inhibitor lapatinib, and the antiangiogenic monoclonal antibody bevacizumab. Trastuzumab, administered with chemotherapy or as a single agent, is indicated for women with HER2-positive disease who are eligible for chemotherapy; those with HR-positive disease should first complete all hormonal therapy options (NCCN, 2011). Following progression on a first-line trastuzumab-containing regimen, trastuzumab should be continued into the next line of treatment (Mannocci et al., 2010; NCCN, 2011). Continuation of trastuzumab plus capecitabine showed a significant improvement in overall response and time to progression compared with capecitabine alone in women with HER2-positive breast cancer who experienced progression during trastuzumab treatment (von Minckwitz et al., 2009), although the benefit did not translate into improved overall survival (von Minckwitz et al., 2011). However, patients who continued or restarted anti-HER2 treatment (trastuzumab or lapatinib) after second progression had significantly longer postprogression survival compared with those who did not receive such treatment (von Minckwitz et al., 2011).

Similarly, women who received trastuzumab in early-stage disease still are eligible to receive trastuzumab in the metastatic setting (NCCN, 2011). Alternatively, a regimen of lapatinib plus capecitabine may be used for HER2 blockade following disease progression on prior trastuzumab therapy (Cameron et al., 2008; Geyer et al., 2006; NCCN, 2011). The combination of lapatinib plus trastuzumab (without chemotherapy) also is an option after multiple trastuzumab-containing regimens (Blackwell et al., 2010).

Bevacizumab initially was approved for use with first-line paclitaxel in MBC regardless of HR or HER2 status after showing that the addition of bevacizumab to weekly paclitaxel significantly extended progression-free survival compared with paclitaxel alone (11.8 versus 5.9 months, hazard ratio = 0.6, p < 0.001) (Miller et al., 2007). A meta-analysis of five randomized trials demonstrated that bevacizumab added to chemotherapy significantly improved progression-free survival, but not overall survival, compared with chemotherapy alone (Valachis et al., 2010). The lack of survival benefit combined with the potential for serious adverse events led the U.S. Food and Drug Administration (FDA) to reevaluate the drug’s MBC indication and withdraw approval of bevacizumab for this setting (FDA, 2011).

Treatment Options Following Resistance

Resistance Mechanisms

Resistance to cytotoxic agents may occur by several mechanisms. The overexpression of the P-glycoprotein efflux pump confers resistance to multiple drug classes, including anthracyclines, taxanes, and vinca alkaloids (Fojo & Menefee, 2007) (see Figure 2). Resistance to doxorubicin also may occur by overexpression of another drug transporter, MRPI (or ABCC1) (Fojo & Menefee, 2007). Taxanes stabilize microtubules by binding reversibly to β-tubulin, but bind less effectively to the βIII-tubulin isoform; overexpression of βIII-tubulin can confer taxane resistance (Kamath, Wilson, Cabral, & Jordan, 2005). In several MBC cohorts, higher βIII-tubulin expression has been associated with disease progression (Paradiso et al., 2005; Tommasi et al., 2007). In a study by Tommasi et al. (2007) (N = 92), disease progression during paclitaxel therapy occurred at higher rates in patients with high versus low tumor βIII-tubulin levels (35% versus 7%, p < 0.002) (Tommasi et al., 2007).

Single Agents

After a patient has progressed following treatment with an anthracycline and a taxane, treatment options that are not susceptible to the same resistance mechanisms are needed. Capecitabine frequently is used in this setting; a dose of 1,250 mg/m² twice daily for 14 days followed by a seven-day rest period produced objective response rates of 15%–28% (Blum et al., 1999, 2001; Fumoleau et al., 2004; Reichardt et al., 2003). Other comparably active single agents are gemcitabine and vinorelbine (Ferrazzi & Stievano, 2006; Modi et al., 2005; Spielmann et al., 2001; Zelek et al., 2001).

Ixabepilone is the first clinically available member of the epothilone class, which stabilizes microtubules by interacting with tubulin in a manner distinct from the taxanes (Rivera, Lee, & Davies, 2008; Vahdat, 2008). Ixabepilone has a low susceptibility to common resistance mechanisms and retains activity in taxane-resistant cell lines (Lee et al., 2001, 2009). The clinical activity of single-agent ixabepilone was demonstrated in a series of phase II trials; ixabepilone at a dose of 40 mg/m² once every three weeks produced an objective response rate of 11.5% and stable disease in 50% of patients (N = 126) (Perez et al., 2007). On the basis of that trial, single-agent ixabepilone was approved by the FDA following previous treatments with an anthracycline, a taxane, and capecitabine (Bristol-Myers Squibb, 2011). Eribulin is a microtubule inhibitor with a mechanism distinct from taxanes, epothilones, and vinca alkaloids (Eisai, Inc., 2012). Eribulin produced objective response rates of 11.5% and 9.3% in heavily pretreated patients with MBC (Cortés et al., 2010; Vahdat et al., 2009) and subsequently was compared with the investigator’s choice of treatment (mainly single-agent vinorelbine, gemcitabine, or capecitabine) in a phase III trial of patients who had received at least two prior regimens for advanced disease including an anthracycline and a taxane (Cortés et al., 2011). Eribulin at a dose of 1.4 mg/m² on days 1 and 8 of a three-week cycle significantly improved overall survival compared with the control group (13.1 versus 10.7 months, p = 0.04), and produced a trend for longer progression-free survival (3.7 versus 2.2 months, p = 0.09). The objective response rate also favored the eribulin arm (12% versus 5%, p = 0.005). Another phase III trial comparing eribulin versus capecitabine in patients with MBC previously treated with an anthracycline and a taxane is ongoing (Twelves et al., 2010).

Combination Therapy

Efforts to improve treatment responses following failure of an anthracycline and a taxane have led to evaluation of combination regimens. Few randomized, controlled trials have found advantages for chemotherapy doublets versus single-agent therapy in this setting (Jassem, Carroll, Ward, Simpson, & Hind, 2009). In a phase III trial, gemcitabine plus vinorelbine significantly
prolonged median progression-free survival compared with vinorelbine alone in women previously treated with an anthracycline and a taxane to six and four months, respectively (p = 0.003) (Martin et al., 2007). Objective response rate tended to be higher in the combination arm (36% versus 26%, p = 0.09), but overall survival did not differ (15.9 versus 16.4 months, p = 0.8). Grade 3 or 4 nonhematologic toxicities occurred at similar rates between treatment arms, but neutropenia was more common in the combination arm.

Ixabepilone plus capcitabine significantly prolonged progression-free survival compared with capcitabine alone in two phase III trials. The first study enrolled taxane-resistant patients pretreated with or resistant to anthracyclines (Thomas, Gomez, et al., 2007). Median progression-free survival was prolonged to 5.8 months compared with 4.2 months for captitabine alone (p = 0.0005). Objective response rate was significantly higher with the combination (35% versus 14%, p < 0.001). Overall survival favored the combination, but the difference was not statistically significant (12.9 versus 11.1 months, p = 0.19) (Hortobagyi et al., 2010). The second trial enrolled patients with MBC who had been treated previously with an anthracycline or a taxane but were not necessarily resistant to those agents (Sparano et al., 2010). Again, ixabepilone plus capcitabine significantly improved progression-free survival (6.2 versus 4.2 months, p < 0.001) and objective response rate (43% versus 29%, p < 0.001) versus single-agent capcitabine, but not overall survival (16.4 versus 15.6 months, p = 0.12). When adjusted for higher occurrence of patients with impaired performance status in the combination arm (32% versus 25%) and other prognostic factors, overall survival difference favoring the combination arm reached statistical significance (hazard ratio = 0.85, 95% confidence interval [0.75, 0.98], p = 0.02).

Those findings indicate that specific chemotherapy doublets may be viable options for single-agent therapy following previous treatment with an anthracycline and a taxane. The ixabepilone-capcitabine doublet following previous treatment with an anthracycline and a taxane has been approved by the FDA (Bristol-Myers Squibb, 2011).

**Trends in Clinical Practice**

**Combination Versus Sequential Therapy**

Several factors influence treatment choices in clinical practice, including treatment history, aggressiveness and extent of disease, biomarker status, patient fragility, and patient preferences.

**Patient- and disease-related factors determine therapeutic approach** (Cardoso et al., 2009). Combination chemotherapy may be preferable for patients with rapid disease progression, life-threatening visceral metastases, or the need to achieve symptomatic control. A sequential single-agent approach that achieves disease stabilization with lower toxicity may be preferable in patients with comorbid conditions.

**Treatment Challenges**

Estrogen receptor and progesterone receptor expression indicate patients who may benefit from hormonal therapy, and HER2 expression identifies patients who may benefit from trastuzumab and lapatinib. However, about 15% of patients have triple-negative breast cancer with tumors that lack estrogen receptor, progesterone receptor, and HER2 expression and, therefore, are not candidates for hormonal therapy or HER2-targeted agents (Foulkes, Smith, & Reis-Filho, 2010).

Triple-negative breast cancer has an aggressive phenotype resembling that of basal-like tumors and tumors carrying BRCA1 or BRCA2 mutations (Atchley et al., 2008; Foulkes et al., 2010) associated with defects in DNA repair (Guler et al., 2011; Zhang & Powell, 2005). That raises the possibility that triple-negative breast cancer may be sensitive to DNA-damaging cytotoxic agents (Anders & Carey, 2009; Telli & Ford, 2010). Triple-negative breast cancer is highly sensitive to anthracycline-based chemotherapy and possibly to platinum-based therapy. Platinum doublets with gemcitabine are active in MBC (Laessig et al., 2007; Nagourney et al., 2008; Yardley et al., 2008), and retrospective analyses suggest that those combinations may be more effective in triple-negative breast cancer compared with non-triple-negative breast cancer subtypes (Koshy, Quispe, Shi, Mansour, & Burton, 2010). Additional evidence of the chemosensitivity of triple-negative breast cancer to platinum-based therapy has been obtained in the neoadjuvant setting (Frasci et al., 2009; Silver et al., 2010; Torrisi et al., 2008). Those findings suggest that a platinum-based regimen may be a suitable option for patients with metastatic triple-negative breast cancer.

Ixabepilone is another option for patients with triple-negative breast cancer. In a retrospective analysis of five phase II trials, objective response rates with single-agent ixabepilone in patients with triple-negative breast cancer were comparable to those for the entire study cohorts (Perez, Patel, & Moreno-Aspitia, 2010).

Understanding the defects inherent in triple-negative breast cancer may lead to further improvements in treatment for that
substance; two promising strategies in clinical trials are PARP-1 (poly[adenosine diphosphate ribose] polymerase-1) inhibitors and epidermal growth factor receptor-targeting agents (Hudis & Gianni, 2011).

Managing Treatment-Related Adverse Events

Treatment-related adverse events are common during therapy with cytotoxic drugs. A proactive approach should be taken to prevent or minimize their impact on the delivery of treatment. Nurses serve as patient advocates and are instrumental in detecting, managing, and documenting adverse events.

Nonhematologic toxicity: Anthracyclines cause dose-cumulative cardiotoxicity. Most clinicians limit the cumulative dose of doxorubicin at 550 mg/m² or at 450 mg/m² for patients with hypertension and those who have received prior chest radiotherapy; patients should be monitored routinely by noninvasive cardiac imaging (Pfeffer, Tziros, & Katz, 2009). For patients with MBC who have already received a cumulative dose of doxorubicin higher than 300 mg/m² or epirubicin higher than 550 mg/m², adjuvant therapy with the cardioprotectant dexrazoxane may be used (Hensley et al., 2009). Once the cumulative dose limit for anthracyclines has been reached, alternative cytotoxic chemotherapy should be considered.

Trastuzumab also causes cardiotoxicity, and the incidence increases with or after anthracycline-based therapy (Walker, Singal, & Jassal, 2009). Although the risk of cardiotoxicity is not related to the cumulative dose, preventative measures used for anthracyclines also are relevant during trastuzumab therapy.

Peripheral neuropathy is a treatment-related adverse event associated with microtubule-stabilizing drugs, including taxanes and ixabepilone (Lee & Swain, 2006). The onset of neuropathy depends on the cumulative dose, generally appearing after three to six cycles of treatment. As expected, the occurrence of grade 3 or 4 peripheral neuropathy with ixabepilone is less common in patients treated in the earlier line setting compared with heavily pretreated patients in the metastatic setting (Baselga et al., 2009; Denduluri et al., 2007; Low et al., 2005; Perez et al., 2007; Roché et al., 2007; Sparano et al., 2010; Thomas, Gomez, et al., 2007; Thomas, Tabernero, et al., 2007). Patients should be monitored carefully for early signs of neuropathy, including paresthesia, numbness, burning, discomfort, or pain. In general, healthcare providers should withhold treatment if grade 2 or higher neuropathy develops, then resume treatment at a reduced dosage once it improves to at least grade 1. That strategy is illustrated by dose reduction guidelines for ixabepilone (Yardley, 2009) (see Figure 3). By using that algorithm, peripheral neuropathy caused by ixabepilone generally is reversible; following dose reduction, 87% of patients receiving ixabepilone monotherapy and 80% of those receiving ixabepilone plus capecitabine had improvement or no further worsening of symptoms (N = 501) (Bristol-Myers Squibb, 2011). In addition, data suggested that early ixabepilone dose reductions do not affect the overall efficacy of ixabepilone in patients with MBC who received four or more courses of ixabepilone plus capecitabine (Valero et al., 2010). Besides dose reduction, symptomatic relief may be achieved with agents useful against neuropathic pain, such as gabapentin and amitriptyline, and by members of the vitamin B complex (Lee & Swain, 2006; Yardley, 2009). Hand-foot syndrome is the dose-limiting toxicity associated with capecitabine. It occurs in about 50%–60% of patients with MBC, including 15%–20% with grade 3 toxicity (Gressett, Stanford, & Hardwicke, 2006; Milano et al., 2008). In clinical trials, hand-foot syndrome developed by a median of three to four cycles (Genentech, Inc., 2011). Patients treated with capecitabine should be monitored for early signs and symptoms, including erythema, skin peeling, numbness, tingling, or burning on the palms of the hands or soles of the feet. Once detected, patients should use topical emollients and creams and avoid extremes in temperature, pressure, and friction on the skin (Lassere & Hoff, 2004). Capecitabine treatment should be interrupted if grade 2 or higher hand-foot syndrome occurs and resumed once symptoms resolve or decrease to grade 1 (Genentech, Inc., 2011). The incidence and severity of hand-foot syndrome are unaffected by concomitant administration of capecitabine with ixabepilone or docetaxel (O’Shaughnessy et al., 2002; Thomas, Gomez, et al., 2007).

Hematologic toxicity: Myelosuppression is a common adverse event with cytotoxic chemotherapy. Frequent monitoring of blood cell counts is recommended, and subsequent treatment cycles should be delayed in the event of persisting toxicity. Treatment generally is resumed when neutrophil counts are 1,500 cells/mm³ or higher and platelet counts are 100,000 cells/mm³ or higher. Depending on the extent of myelosuppression, doses may be reduced or growth factor support provided in subsequent cycles. Dose reductions for paclitaxel and docetaxel are recommended in the event of grade 4 neutropenia lasting seven or more days or febrile neutropenia (Bristol-Myers Squibb, 2010; sanofi-aventis U.S. LLC, 2010). Several factors influence treatment choices in clinical practice, including treatment history, aggressiveness and extent of disease, biomarker status, patient fragility, and patient preferences.

New Treatments in Development

Trastuzumab Emtansine

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate that combines trastuzumab with the microtubule-disrupting maytansine derivative DM1 (Niculescu-Duvaz, 2010); it targets delivery of DM1 only to HER2-expressing tumor cells. Preclinical studies showed that T-DM1 has greater activity than trastuzumab itself and retains activity in HER2-positive breast cancer cell lines resistant to trastuzumab or lapatinib (Juntila, Li, Parsons, Phillips, & Slwikowski, 2011; Lewis Philips et al., 2008). T-DM1 was well tolerated in those studies; the most common grade 3 or 4 adverse event in 107 patients was thrombocytopenia (7%). Those findings suggest that T-DM1 may be an option for patients with HER2-positive MBC. T-DM1 is in phase II and III clinical trials.

Pertuzumab

Pertuzumab is a humanized monoclonal antibody that binds to a different HER2 epitope than trastuzumab, inhibiting HER2-mediated dimerization and potentially blocking signaling via
multiple pathways, including epidermal growth factor receptor and HER3 (Scheuer et al., 2009). The binding of pertuzumab to HER2 is not impaired by pretreatment with trastuzumab, supporting their use in combination therapy (Nahta, Hung, & Esteva, 2004; Scheuer et al., 2009). Results from the randomized phase III CLEOPATRA study of 808 first-line patients with HER2-positive MBC showed that the addition of pertuzumab to trastuzumab and docetaxel improves independently assessed progression-free survival compared with trastuzumab and docetaxel alone (18.5 versus 12.4 months, hazard ratio = 0.62, p < 0.001). In addition, the study showed a strong trend in extending overall survival based on an exploratory interim analysis (Baselga et al., 2012).

Cetuximab

The anti–epidermal growth factor monoclonal antibody cetuximab may be a targeted approach for the treatment of patients with triple-negative breast cancer; 30%-50% of those patients have tumors that overexpress epidermal growth factor receptor (Lerma et al., 2007; Pintens et al., 2009; Thike et al., 2010). Cetuximab had limited single-agent activity in patients with metastatic triple-negative breast cancer (Carey et al., 2008). Cetuximab has been approved by the FDA for treatment of head and neck and colorectal cancers and currently is in phase II development in breast cancer. Trials, to date, are targeting patients with basal-like tumors or triple-negative breast cancer.

Poly(Adenosine Diphosphate Ribose) Polymerase-1 Inhibitors

PARP-1 is a key enzyme in the base excision repair pathway for single-strand DNA breaks, which plays a key role in repairing double-strand breaks when high-fidelity homologous recombination is defective, such as in patients with BRCA1 mutations.

FIGURE 3. Dose Reduction Guidelines for Ixabepilone

and potentially in those with triple-negative breast cancer (Annunziata & O’Shaughnessy, 2010; Comen & Robson, 2010). The PARP-1 inhibitors olaparib and veliparib currently are in clinical development (Tutt et al., 2010). Iniparib, originally considered a PARP-1 inhibitor, showed promising early results in combination with chemotherapy in patients with triple-negative breast cancer (O’Shaughnessy, Osborne, et al., 2011). However, those results were not confirmed in a large phase III trial (O’Shaughnessy, Schwartzberg, et al., 2011) and observations suggest that iniparib’s primary mechanism of action may not be PARP-1 inhibition (Liu et al., 2012; Patel et al., 2012).

Conclusions

Current treatment of MBC is influenced by multiple factors including biomarker status and treatment history. Patients with HR-positive disease initially are treated with hormonal therapy, whereas those with HER2-positive disease are treated with trastuzumab and lapatinib in conjunction with chemotherapy. In contrast, treatment of patients with triple-negative breast cancer depends only on cytotoxic chemotherapy.

Anthracyclines and taxanes are among the most active cytotoxic drugs for breast cancer, but their use in early-stage disease may compromise their use in the metastatic setting, and the development of resistance or toxicity requires alternative therapies. Many cytotoxic agents are useful following anthracycline and taxane treatment. Proactive management to detect treatment-related adverse events while they are mild to moderate in severity remains important to ensure effective treatment delivery.

Multiple agents are in development that eventually may be useful in future treatment of MBC, with several targeted to the subset with triple-negative breast cancer. As advances are made in identifying subtypes of patients with MBC, biomarkers are expected to be identified to help tailor treatment, thus maximizing patient outcome. Although MBC remains incurable and the primary goal of current therapies mostly is to provide disease control and palliation, the individualized use of novel drugs and their combinations based on tumor molecular characteristics may cause MBC to become a chronic disease.

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