

# Current Approaches and Unmet Needs in the Treatment of Metastatic Breast Cancer

**DESPITE RECENT ADVANCES** in treatment, metastatic breast cancer (mBC) remains one of the leading causes of cancer-related deaths in the United States among women.<sup>1</sup> The prevalence of mBC has also been increasing; almost 170,000 women are estimated to be living with the disease in 2020.<sup>2</sup> The prognosis for women with mBC remains poor. Although there has been an improvement in mBC survival in the past few decades, the 5-year survival rate remains low at 28% compared with 86% to 99% among women with localized or regional breast cancer.<sup>1,2</sup>

## Current Treatment Options for Metastatic Breast Cancer

The treatment goals of mBC are to ameliorate symptoms, maintain quality of life, and prolong overall survival (OS).<sup>3,4</sup> Management of mBC is based on tumor expression of estrogen receptor (ER), progesterone receptor (PR), and HER2 receptors.<sup>1</sup> For frontline therapy in the metastatic setting in hormone receptor (HR)-positive mBCs that are ER positive or PR positive, hormone therapy with either a selective ER downregulator (fulvestrant) or an aromatase inhibitor forms the foundation of treatment. If the HR-positive mBC is HER2 negative, the preferred regimen is hormone therapy combined with a CDK4/6 inhibitor. In HR-positive/HER2-positive mBC, HER2-directed therapy (trastuzumab and/or lapatinib) in combination with hormone therapy is primarily recommended.<sup>1</sup>

In HR-negative mBC, cytotoxic chemotherapy remains the backbone of treatment regimens.<sup>1,3</sup> In HR-negative/HER2-positive mBC in the frontline setting, HER2-targeted therapy (pertuzumab plus trastuzumab) combined with docetaxel or paclitaxel is the preferred regimen.<sup>1</sup> In subsequent lines, other cytotoxic chemotherapy agents are combined with HER2-targeted therapy. Treatment options for triple-negative breast cancer (TNBC), which is ER negative, PR negative, and HER-negative, are more limited because of the lack of therapeutic targets.<sup>3</sup> In TNBC, sequential, single-agent cytotoxic chemotherapy remains the primary option in the frontline and later-line settings. In patients with TNBC and high tumor burden, visceral crisis, or rapidly progressing disease, chemotherapy combinations may be considered.<sup>1</sup>

Recent trials of immunotherapy and *BRCA* mutation-targeted therapy in TNBC have shown some promise. In the phase 3 double-blind, placebo-controlled IMpassion130 trial (NCT02425891), the PD-L1 inhibitor atezolizumab improved progression-free survival (PFS) when combined with albumin-bound (nab)-paclitaxel compared with nab-paclitaxel alone in metastatic TNBC.<sup>5</sup> In the intention-to-treat population, which included patients with and without PD-L1 cell positivity, the addition of atezolizumab to nab-paclitaxel led to a PFS of 7.2 months compared with 5.5 months in the placebo group (hazard ratio 0.80; 95% CI, 0.69-0.92;  $P = .0021$ ). In patients with positive PD-L1 expression, median PFS was 7.5 months and 5.3 months in the atezolizumab and placebo groups, respectively (hazard ratio 0.63; 95% CI, 0.50-0.80;  $P < .0001$ ).<sup>5</sup> Overall survival (OS) in the intention-to-treat population was not significantly different between the arms (21.0 months vs 18.7 months; hazard ratio 0.86; 95% CI, 0.72-1.02;  $P = .078$ ).<sup>5</sup> In an exploratory analysis, patients without PD-L1 tumors did not have OS benefit. However, among patients with PD-L1-positive tumors,

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median OS was 25.0 months with atezolizumab and 18.0 months with placebo (hazard ratio 0.71; 95% CI, 0.54-0.94).<sup>5</sup> Atezolizumab was approved in 2019 for patients with locally advanced or metastatic TNBC who have PD-L1-expressing tumors when used in combination with nab-paclitaxel.<sup>6,7</sup>

Sacituzumab govitecan-hziy was also recently approved for patients with metastatic TNBC who have received at least 2 prior lines of therapy in the metastatic setting.<sup>8</sup> Sacituzumab govitecan-hziy is an antibody-drug conjugate that contains an antibody that targets Trop-2, a glycoprotein overexpressed in many epithelial cancers, including TNBC.<sup>9,10</sup> The monoclonal antibody delivers the toxic payload SN-38, an active metabolite of irinotecan, to the tumor microenvironment and intracellularly.<sup>9,10</sup> Approval of this agent was based on results of a phase 1/2 single-group multicenter trial in 108 patients with metastatic TNBC.<sup>11</sup> Included patients were heavily pretreated with a range of 2 to 10 previous lines of anticancer regimens (median = 3).<sup>11</sup> After a median of 9.7 months of follow-up, the response rate was 33.3%, and the clinical benefit rate, which included patients with stable disease for 6 months or more, was 45.4%.<sup>11</sup> The median PFS was 5.5 months (95% CI, 4.1-6.3).<sup>11</sup>

### Challenges and Unmet Needs

In HR-negative mBC, chemotherapy remains the backbone of treatment regimens. The majority of recommended regimens contain agents requiring intravenous (IV) infusion or intramuscular administration (fulvestrant). The only oral agents are cyclophosphamide, capecitabine, tucatinib, lapatinib, and neratinib.<sup>1</sup> Despite the number of treatment options for patients with mBC, unmet needs remain pertaining to disease control, prolonging the interval to intensive cytotoxic therapy, and treatment-related complications. Additionally, there is a greater need for treatment regimens that are less burdensome for patients and their caregivers, as well as reducing health care costs associated with the IV administration of anticancer regimens.

### Disease Control

The past decade has marked dramatic progress in biomarker-based treatment in mBC. However, progress in the treatment of metastatic TNBC is limited by the lack of therapeutic targets. Effective therapy for patients with metastatic TNBC is an unmet need.<sup>3</sup> The recent approvals of atezolizumab for PD-L1-expressing metastatic TNBC and sacituzumab govitecan-hziy for patients with TNBC who have received at least 2 prior lines of therapy in the metastatic setting have expanded the options for this patient group. However, mBC eventually will progress in most patients.<sup>6,8</sup> There is an immense medical need for new treatment options to prolong the interval to starting

intensive cytotoxic therapy, which has potentially serious adverse effects (AEs) that can reduce the quality of life.<sup>12</sup>

Metronomic therapy has been explored to prolong the interval in the need for intensive cytotoxic therapy. Metronomic therapy is the frequent, long-term administration of chemotherapy at low doses without a break in therapy.<sup>13</sup> Metronomic therapy maintains plasma concentration of the cytotoxic agent above the therapeutic threshold but substantially below the maximum tolerated dose. Data suggest metronomic therapy may inhibit angiogenesis and have antiproliferative and immunomodulatory activities.<sup>12</sup> There is also possible synergy with molecularly targeted agents.<sup>13</sup> Hence, metronomic therapy may be able to improve the therapeutic index of cytotoxic agents by decreasing treatment-associated toxicities and exerting disease control activity.<sup>12</sup> In mBC, studies of metronomic therapy have included oral vinorelbine and cyclophosphamide.<sup>13</sup> The addition of metronomic oral cyclophosphamide to pertuzumab plus trastuzumab in older patients with HER2-positive mBC improved PFS by 7 months compared with pertuzumab plus trastuzumab alone (12.7 months; 95% CI, 6.7-24.8 months vs 5.6 months; 95% CI, 3.6-16.8 months).<sup>14</sup>

Although metronomic therapy has the potential to increase antitumor efficacy while limiting chemotherapy-related toxicity, advancing the field of metronomic chemotherapy would require the development of oral cytotoxic agents. Oral agents, unlike IV ones, can eliminate the logistical barriers for chemotherapy to be administered as a continuous/frequent low-dose regimen. In addition, the development of oral chemotherapy agents will facilitate further clinical trials to evaluate the efficacy and toxicity of metronomic oral therapy in patients with mBC.

### Treatment-Related Complications

Taxanes are widely used in mBC, but they are highly hydrophobic and insoluble.<sup>15</sup> To make parenteral administration possible, polyoxyethylated castor oil and ethanol are used as the vehicle for paclitaxel, and polysorbate 80 and ethanol are used as the vehicle for docetaxel.<sup>15</sup> These solvents lead to hypersensitivity reactions and prolonged peripheral neuropathy that may be irreversible.<sup>15</sup> Patients receiving paclitaxel require premedication with corticosteroids, H<sub>2</sub>-receptor antagonists, and diphenhydramine. Despite premedication, fatal hypersensitivity reactions have occurred in patients receiving IV paclitaxel.<sup>16</sup> Additionally, patients with certain comorbidities (eg, diabetes) may not tolerate corticosteroid premedication, which can lead to hyperglycemia requiring intensive glycemic control and monitoring.

Besides hypersensitivity reactions, the taxanes' solvent vehicles may directly contribute to neutropenia. In a clinical trial comparing nab-paclitaxel and conventional

paclitaxel, among patients treated with nab-paclitaxel, treatment-related grade 4 neutropenia was significantly lower than conventional paclitaxel (9% vs 22%,  $P < .001$ ) despite a higher dose, suggesting that the polyoxyethylated castor oil vehicle may be partly responsible for the neutropenia associated with paclitaxel.<sup>15</sup> Recent studies of oral paclitaxel without solvent vehicles also demonstrated a decreased incidence of peripheral neuropathy and alopecia.<sup>17</sup> Additionally, solvents may decrease the efficacy of taxanes because of entrapment of the active drug in micelles within the patient's plasma, leading to increased systemic exposure and inadequate dose-dependent antitumor activity.<sup>15</sup>

Chemotherapy also may be poorly tolerated, especially in the older population. Avoiding significant toxicities and maintaining quality of life may be just as important as prolonging survival in mBC.<sup>14</sup> Because of the lower potential for toxicity while maintaining efficacy, oral metronomic chemotherapy at frequent, low doses is an attractive treatment option for older patients with cancer who are not suitable candidates for conventional chemotherapy.<sup>13</sup> Indeed, a meta-analysis of patients treated by metronomic chemotherapy for various tumor types indicated that grade 3 or 4 AEs were rare (eg, neutropenia, 5.39%; anemia, 1.73%; febrile neutropenia, 0.53%).<sup>18</sup>

Complications of IV access sites also are a concern with chemotherapies administered by IV infusion. With chronic venous and/or central line access, access-related complications are not uncommon, including sclerosis of the veins (31%), extravasation (7%-17%), access-related infections (6%-13%) and catheter-associated thrombosis (6%-18%).<sup>19</sup> Furthermore, patients are concerned about the pain associated with IV placement and the IV site. In a survey, 47.4% of patients with breast cancer reported apprehension about IV line–related pain, and 65.7% were concerned about problems locating a vein for infusion.<sup>20</sup>

During the coronavirus disease 2019 (COVID-19) epidemic, the American Society of Clinical Oncology has encouraged physicians to use telemedicine to help exposure to and transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In addition, patients with COVID-19 should be symptom-free before receiving in-office IV therapy.<sup>21</sup> Because of concerns regarding infusion-related AEs, disposal of cytotoxic agents, and risk of SARS-CoV-2 exposure to medical staff, home infusion generally is not recommended.<sup>21</sup> Effective oral chemotherapy regimens, if widely available, could potentially play a substantial role in preventing transmission of SARS-CoV-2.

### Patient Preference

The current mechanisms for delivery of treatment options present significant burdens for patients. One of

the often overlooked considerations is the impact of a chemotherapeutic regimen on a patient's daily life. With an IV regimen—besides the actual time patients and/or caregivers spend at the infusion clinic—patients must travel to and from the clinic and wait for their treatment to be administered.<sup>22</sup> The time commitment interferes with the patients' and caregivers' work obligations and other responsibilities. Additionally, practical concerns exist regarding travel to and from infusion clinics. For example, in a survey study, 55.4% of patients worried about having nausea during their trip home after chemotherapy infusion.<sup>20</sup>

One solution is the use of oral chemotherapy that patients can administer at home. Findings from a survey study of 224 patients with breast cancer receiving either oral chemotherapy ( $n = 60$ ) or IV chemotherapy ( $n = 164$ ) revealed that 48.3% of patients receiving oral treatments believed they were more able to handle the disease.<sup>23</sup> Approximately 60% of patients stated that an oral regimen gave them more autonomy outside the clinic.<sup>23</sup> Similarly, in another survey study of 59 patients with breast cancer starting oral chemotherapy, findings showed that 67% of the patients perceived that an oral chemotherapy regimen would lessen the effort to cope with the disease.<sup>24</sup> These results were echoed by findings from a survey study, in which 73% patients in Spain with metastatic lung or breast cancer who had previously received IV therapy and oral chemotherapy stated that their everyday life would be less affected by oral medications.<sup>20</sup> Among patients with mBC in this study, 66.9% were concerned about inconvenience of an IV regimen.<sup>20</sup>

Because of the interference of IV regimens with patients' daily lives and autonomy, it is no surprise that the majority of patients with breast cancer prefer an oral regimen. In fact, findings from a previously mentioned study showed that 76% of patients preferred an oral regimen administered at home instead of infusion at a clinic.<sup>20</sup> In an internet-based cross-sectional survey study in the United States, women with breast cancer were asked to indicate the acceptability of various AEs and regimens of different frequency and duration of administration.<sup>25</sup> Most of the participants (77%) preferred an oral regimen compared with 19% who were willing to choose a less convenient regimen.<sup>25</sup> In a utility analysis using a similar internet-based survey design, patients with breast cancer were asked to trade off the preferred oral administration in exchange for a reduction in AEs (eg, alopecia, neutropenia).<sup>26</sup> Results showed that patients were willing to tolerate a 5% increased risk of alopecia or grade 1 to 2 hand-foot syndrome in exchange for an oral regimen.<sup>26</sup> In general, the more infusion days per treatment cycle and the longer the infusion time (eg, 3 hours vs 30 minutes), the less willing patients were to tolerate such a regimen.<sup>26</sup>

In a review of literature on patient preference on the modes of cancer treatment administration, reasons for patients' preference for oral chemotherapy regimens included the ability to take the therapy at home, convenience, desire to continue working, impact on daily life and relationships, autonomy, and an increased ability to cope with the disease.<sup>27</sup> However, patients are generally not willing to accept reduced efficacy or increased treatment-related toxicity in exchange for a convenient regimen.<sup>27</sup>

### Costs

Costs associated with IV chemotherapy can be substantial. Treatment with IV chemotherapy entails not only drug acquisition cost but also costs related to specialized supplies and equipment, personnel needed to prepare and administer the IV drug, and management of AEs related to IV administration.<sup>28</sup> In an administrative database study, investigators evaluated costs associated with IV chemotherapy administration in 828 patients with mBC during 7406 visits for single-agent IV therapy.<sup>28</sup> IV administration constituted 10% to 11% of the overall cost of therapy, and other visit-related services (eg, antihypercalcemic agents, hematopoietic support, anticancer drugs used off label) accounted for 31% to 32% of costs.<sup>28</sup> Although the costs of IV administration were approximately one-tenth of overall therapy costs, they could have been avoided with the use of oral regimens.<sup>28</sup> The authors hypothesized that even if an all-IV multiagent therapy were replaced with an oral plus IV regimen, some costs related to IV administration could still be avoided.<sup>28</sup> In a more recent study assessing health care costs in patients with stage 0 to IV breast cancer and service types, costs associated with the day of chemotherapy accounted for more than 25% to 26% of total costs.<sup>29</sup>

Direct comparisons of health care costs between IV and oral chemotherapy have also been reported. In a population-based study, investigators compared the relative cost impact among women starting capecitabine (oral regimen, n = 114) versus taxanes (IV regimen, n = 619) as first-line chemotherapy for mBC from 1998 to 2002.<sup>22</sup> Participants were identified from the North Carolina Central Cancer Registry and Medicaid claims linked databases, and their claims were followed through 2005.<sup>22</sup> In the first year after starting the respective first-line therapies, women receiving IV taxanes had higher total health care utilization compared with those who received oral capecitabine (\$43,353 vs \$35,842;  $P = .0089$ ). The cost differences were mainly due to higher outpatient costs associated with IV taxanes ( $P < .001$ ).<sup>22</sup> After adjusting for confounders, health care costs associated with oral capecitabine were 32% lower compared with IV taxanes ( $P = .0001$ ).<sup>22</sup>

In another study, investigators conducted a budget impact model comparing the health care costs associated

with trastuzumab-based therapy (IV regimen) vs lapatinib plus capecitabine (oral regimen) among an estimated 43,707 patients with mBC in the French national hospital database.<sup>30</sup> Despite slightly lower drug acquisition costs for the IV regimen, the 1-year treatment cost per patient was 2 times higher for the IV regimen compared with the oral regimen when costs included administration and nondrug expenditures.<sup>30</sup> Estimated annual cost difference between the IV and oral regimens was €90.8 million.<sup>30</sup> Use of an oral regimen also would lead to 25,357 fewer outpatient hospitalizations for chemotherapy administration, resulting in substantial savings in hospital and transportation costs.<sup>30</sup>

### Summary

There have been many recent advances in the treatment of mBC. The current mechanisms for delivery of these options, however, present significant burdens for patients. In addition, some IV formulations of taxanes, which are frequently used in the management of patients with mBC, may directly contribute to treatment toxicities and complications. The need for IV administration for most chemotherapy regimens increases health care costs. New approaches and delivery mechanisms are needed to optimize outcomes and maintain the quality of life in patients with mBC. ♦

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