

IMPLICATIONS OF ORAL THERAPY IN METASTATIC BREAST CANCER: CONSIDERATIONS FOR DELIVERY NETWORKS

A STAKEHOLDER INTERCHANGE REPORT

Despite significant advances in treatment, metastatic breast cancer (mBC) remains the second leading cause of cancer-related death in women in the United States.¹ In 2020, it was estimated that in the United States, 276,480 women would receive a diagnosis of invasive breast cancer and 42,170 women would die of breast cancer.¹ The overall 5-year survival rate for mBC is 27%, but rates are roughly 9% lower in Black women compared with White women.¹ The prevalence of women living with mBC has consistently risen since 1990 and was projected to increase by 31% between 2010 and 2020.² This increase can partially be explained by increased median survival after diagnosis of mBC.²

Breast cancer treatment continues to be a significant financial burden for patients, even those with insurance coverage.³ In fact, approximately one-third of cancer survivors incurred debt related to their cancer treatment, and patients with Medicare spent an average of more than \$8000 out of pocket.³ Breast cancer treatment is also costly for health care payers, with the annual cost per patient paid by Medicare in 2008 estimated at approximately \$12,500 in the first year after diagnosis, \$1400 in subsequent years, and more than \$33,000 in the year leading up to death.⁴ Much of the cost related to mBC treatment is related to the direct cost of the intravenous (IV) chemotherapy agent, as well as to other costs related to drug administration, including the practitioner's time, costs related to the management of adverse effects (AEs) associated with the chemotherapy agent, and the need for equipment, supplies, and other support staff.⁵ Almost one-third of the cost associated with an IV infusion can be attributed to "other services provided at the visit," 99% of which is the cost of drugs required to prevent or treat AEs.^{5,6} Other costs incurred by patients related to the administration of IV chemotherapy include those associated with travel and absence from home, including transportation, parking, meals, telephone calls, housekeeping/laundry services, childcare, and hotel stays.⁴

The American Journal of Managed Care[®] recently convened a stakeholder interchange bringing together leaders in both the clinical and managed care communities to discuss oral therapeutics in the management of mBC. Participants discussed the shift of oncology treatments to oral agents, specifically in mBC; strategies for successful uptake of oral therapies, including the impact of coronavirus disease 2019 (COVID-19); and the incorporation of oral therapy for mBC into a value-based accountable payment model. This article summarizes key points from a discussion led by Bruce Feinberg, DO, vice president and chief medical officer at Cardinal Health Specialty Solutions in Atlanta, Georgia.

MBC TREATMENT LANDSCAPE

Current treatment options for mBC are largely guided by hormone receptor (HR) and human epidermal growth factor receptor 2 (HER2) status. In postmenopausal patients with HR-positive (HR+)/HER2-negative (HER2-) mBC, the category 1 recommendation for first-line treatment is a cyclin-dependent kinase (CDK) 4/6 inhibitor plus an aromatase inhibitor (AI), fulvestrant plus or minus a CDK4/6 inhibitor, or fulvestrant with a nonsteroidal AI.⁷ In patients who are premenopausal, ovarian suppression/ablation should be performed in addition to treatment with the above therapies.⁷

For second-line therapy in postmenopausal patients with HR+/HER2- mBC, the National Comprehensive Cancer Network (NCCN) recommends fulvestrant plus a CDK4/6 inhibitor (if the patient has no prior exposure to CDK4/6 inhibitors)⁷ or fulvestrant with alpelisib if *PIK3CA* mutation is present.⁷ Other options for second-line therapy include everolimus with either an AI, tamoxifen, or fulvestrant; fulvestrant monotherapy; nonsteroidal or steroidal AI monotherapy; or selective estrogen receptor modulator monotherapy.⁷ In patients who progressed on endocrine therapy and had already received several systemic therapies, the CDK4/6 inhibitor abemaciclib is also recommended as monotherapy.⁷ Similarly, lapatinib plus capecitabine or trastuzumab may be considered for HR-/HER2+ disease after progression on a regimen containing trastuzumab.⁷

For patients with HER2+ cancer, treatment recommendations are determined by HR status. In HR-/HER2+ mBC, first-line treatment involves HER2-targeted therapy plus systemic chemotherapy.⁷ Specific recommendations are pertuzumab plus trastuzumab along with a taxane (either docetaxel or paclitaxel) for systemic chemotherapy.^{7,8} If patients with HR-/HER2+ mBC progress on first-line therapy with trastuzumab alone plus chemotherapy, treatment containing both trastuzumab plus pertuzumab with or without a chemotherapeutic agent may be used.⁷ Neratinib plus capecitabine has also been included as a category 2A recommendation in the setting of HR-/HER2+ mBC progressing on at least 2 prior HER2-targeted therapies.⁷ In patients with HR+/HER2+ cancer, first-line treatment includes targeted HER2 therapy plus chemotherapy, endocrine therapy alone, or endocrine therapy combined with HER2-targeted therapies.⁷ In premenopausal patients receiving HER2-targeted therapy in combination with endocrine therapy, ovarian suppression or ablation should occur.⁷ Other combinations of endocrine therapy have been included in the NCCN

recommendations, primarily for use after completion of chemotherapy and HER2-targeted therapy or along with HER2-targeted therapy if continuation is needed for disease control.⁷

For patients with metastatic triple-negative breast cancer (mTNBC), systemic chemotherapy remains the standard of care,⁷ and treatment with sequential single agents is preferred to combination therapy due to increased toxicity and minimal survival benefit associated with combination therapy.⁷ First-line therapy is typically continued until disease progression or unacceptable AEs occur, at which time a different cytotoxic agent can be utilized for monotherapy as a second-line therapy.⁷ This sequential approach can be continued through multiple lines as tolerated, using shared decision-making involving both the treating physician and the patient.⁷

THE EVOLVING TREATMENT LANDSCAPE

More recent research has explored targeted therapy for treatment of mBC in certain cases. For example, in patients with germline *BRCA1/2* mutations, the NCCN guidelines panel has included use of PARP inhibitors as a category 1 recommendation.⁷ In patients with mTNBC and expression of PD-L1 in 1% or more of the immune cells infiltrating the tumor, treatment with a PD-L1 inhibitor in combination with albumin-bound paclitaxel is a category 2A recommendation.⁷ Atezolizumab was approved for this indication in March 2019.^{9,10} Targeted treatment based on a *PI3K* gene mutation has also shown promise with HR+ patients receiving *PI3K* inhibitors in combination with fulvestrant, exhibiting a significant increase in progression-free survival compared with fulvestrant alone.⁷ In patients with mBC who have progressed on prior treatment and have microsatellite instability–high or mismatch repair–deficient tumors, immunotherapy with the checkpoint inhibitor pembrolizumab has been shown to have antitumor activity and is FDA approved for treatment if there are no alternative therapy options.⁷ Antibody-drug conjugates (ADCs) are also being developed to link antigen-targeting agents with cytotoxic drugs, as in the case of ado-trastuzumab emtansine (T-DM1), which is an option for use in patients with HER2+ mBC.⁷ Another ADC, sacituzumab govitecan-hziy, was recently approved for patients with mTNBC who have been treated with at least 2 prior lines of chemotherapy for metastatic disease.¹¹ In patients with the rare *NTRK* gene fusion, *NTRK*-inhibitor therapy

can be considered if there are no alternative treatment options or if disease has progressed on treatment.⁷

Despite significant advances in mBC treatment, chemotherapy continues to be an important component of therapy and is expected to remain as such for the foreseeable future.¹² Taxane-based chemotherapy regimens are commonly used for systemic treatment of breast cancer.¹³ Systemic therapy with a taxane, either docetaxel (category 1) or paclitaxel (category 2A), is recommended first-line therapy in conjunction with HER2-directed therapy in patients with HR-/HER2+ mBC⁷ and is also included in recommendations for first-line treatment of HR+/HER2+ mBC.⁷ The 5th European School of Oncology–European Society of Medical Oncology International Consensus Guidelines for Advanced Breast Cancer also include single-agent taxanes or anthracycline as first-line therapy when chemotherapy is incorporated into the treatment regimen.¹⁴

ADDRESSING CHALLENGES ASSOCIATED WITH CHEMOTHERAPY

Chemotherapy-induced peripheral neuropathy (CIPN) is common with IV taxane therapy and can result in treatment delay, reduction, or discontinuation that negatively affects treatment outcomes.^{15,16} It can also cause persistent pain that results in impairment of activities of daily living and a reduction in quality of life.¹⁵ Taxanes have been associated with rates of CIPN as high as 60%.¹⁷ Taxane-related neuropathy is often cumulative, worsening with each treatment cycle, and often persists after discontinuation of chemotherapy.¹⁵ Patients with CIPN also have increased health care utilization compared with controls, including an increase in hospitalizations (51% vs 37%, respectively), emergency department visits (47% vs 37%), oncology visits (63% vs 55%), and neurology visits (29% vs 6%).¹⁸

Another potential concern with paclitaxel administration is that it requires mixing with Cremophor EL (CrEL), a polyoxyethylated castor oil, before IV administration due to its lipophilic nature.¹⁶ Patients with a history of severe hypersensitivity reactions to other CrEL-containing drugs may not receive IV paclitaxel, and those patients who do receive it must be premedicated with corticosteroids, diphenhydramine, and histamine₂-receptor antagonists due to the significant risk of hypersensitivity to the CrEL.^{16,19} CrEL has also been found to affect the pharmacokinetics of paclitaxel by binding the drug within micelles, resulting in nonlinear drug

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disposition, increased plasma concentration, and decreased relative tissue levels of paclitaxel.¹⁹ Complications related to the need for vascular access are also significant and include sclerosis of the vein, drug extravasation, access-related infections, thrombosis, and pain.^{20,21}

The use of novel delivery systems, such as nanocarriers for chemotherapy administration, has allowed for IV administration of lipophilic substances without the need for toxic solvents such as Cremophor. These carriers allow increased drug circulation time; selective distribution of the drug to the tumor; decreased systemic exposure to the chemotherapy agent; and, in some cases, improved efficacy.²² Some examples of these nanocarriers are liposomal formulations, polymeric micelles, albumin nanoparticles, and polymer conjugates. In general, all these formulations appear to have a good safety profile and allow for higher maximum-tolerated doses than free drug.²² A paclitaxel-containing formulation bound to human serum albumin particles, nab-paclitaxel, has been developed that is Cremophor free.²³ This formulation has been shown to be safe for administration without premedication for hypersensitivity prevention.²³

Although cost-related medication nonadherence occurs among all patients, it is higher in patients who are uninsured or underinsured than in their counterparts with more comprehensive insurance coverage.

Historically, oral bioavailability of paclitaxel has been limited because it is a substrate of the ABCB1 protein, or P-glycoprotein (P-gp), which inhibits intestinal absorption.²⁴ HM30181 is a highly specific and potent P-gp inhibitor developed for the purpose of improving absorption of drugs that are known substrates of P-gp.²⁵ It has been studied in combination with paclitaxel as oral paclitaxel plus HM30181, and a dose of 615mg/m² was shown to have bioavailability of 11.8% in patients, with an area under the curve equivalent to that seen in 80mg/m² weekly IV paclitaxel.²⁶ Oral paclitaxel plus HM30181 also resulted in a favorable toxicity profile related to lower peak plasma levels compared with IV infusion; it was also associated with increased time at therapeutic levels of paclitaxel.²⁶ HM30181 itself has a low bioavailability, which allows for high doses to be given to maximize P-gp inhibition without concern for significant systemic absorption.²⁴

The significance of an oral alternative to IV paclitaxel is especially relevant given that the setting of care has become an increasingly important factor in deciding method of drug delivery. According to one stakeholder, “[T]he concept of setting of care cuts across all infusions. Now with [COVID-19], this becomes a very interesting

opportunity to look at what can be delivered in the home that is safe [and cost-effective].”

According to another stakeholder, “[Setting of care management has] been one of our top initiatives coming into this fiscal year. We’ve seen it mostly [in] nononcology, but now we’re seeing it start to push into oncology, specifically with immunotherapy.”

Because oral paclitaxel plus HM30181 has been shown to result in similar bioavailability to IV paclitaxel, a lower peak plasma concentration, and prolonged therapeutic drug exposure,²⁶ its use could allow for an increase in home-based oncology treatment options. One stakeholder adds that, traditionally, because of the risk of AEs, “[there has been] an issue around...what needs to be monitored [and] what [can] be done in the home setting, [which can include] checking in on the patient within a couple of days, etc. All [of] that’s arranged through case management.”

However, given that oral paclitaxel plus HM30181 is Cremophor free and given by mouth, there is no need for premedication against hypersensitivity reactions, IV access, or treatment in a medical facility.²⁷ Similarly, this oral preparation is associated with a significantly lower risk of peripheral neuropathy and alopecia and a significant improvement in overall response rate compared with IV paclitaxel.²⁷

ORAL TREATMENTS IN MBC: PROS AND CONS

It has been well documented that patients with cancer prefer orally administered treatment to IV provided the efficacy and toxicity profiles are comparable.^{28,29} Some commonly cited reasons for this preference are convenience, ability to receive treatment at home, concerns surrounding the need for IV access and use of needles, quality-of-life issues, ability to cope with one’s disease, and autonomy.^{28,29} Some other benefits of oral chemotherapy include prolonged therapeutic drug exposure, decreased peak plasma concentrations—and, therefore, toxicities—lack of complications related to IV access, avoidance of infusion-related hypersensitivity reactions and the need for premedication, and a resultant decrease in health care utilization.^{26,27}

Oral breast cancer formulations are becoming more common, representing up to 35% of oncology drugs currently in the pipeline.³⁰ Although oral chemotherapy (OC) offers greater convenience, there may be disadvantages to adherence in some patients. It is not uncommon for patients to forget or intentionally skip doses of their medication.³¹ Patients may also take extra doses in a day to compensate for a missed dose or take their scheduled medication despite experiencing dose-limiting AEs.³² AEs are a common reason for patients to reduce their OC dose, either with or without their doctor’s instructions.³¹ Commonly cited AEs resulting in OC reduction include neuropathy, diarrhea, fatigue, nausea, and rash.³¹

One stakeholder noted that the patient cost share also may be an issue. “This is an oral; it’s going to be on the pharmacy benefit. [It] may even be on a specialty tier and may have coinsurance. So certainly, in terms of patient out of pocket, financial toxicity is going to perhaps be a concern.”

Financial concerns also factor into patient adherence, especially since insurance coverage for OC seems to have lagged behind coverage for IV therapies.³³ Although cost-related medication nonadherence occurs among all patients, it is higher in patients who are uninsured or underinsured than in their counterparts with more comprehensive insurance coverage.³⁴

ENSURING SUCCESS OF OC

Management of oral oncolytic therapy, while allowing patients more flexibility and autonomy in their cancer treatment,³⁵ can be challenging for many reasons. Because office visits are not required for drug administration, it may result in fragmentation of care. This affects the ability to monitor for medication tolerability and safety, assess patient adherence, provide patient education, ensure patient access to medication, and monitor the effects of treatment.³⁶

A successful approach to management of patients receiving OC should involve multidisciplinary teams, including the primary provider, specialty pharmacists, and oncology nurses.^{36,37} The prescribing provider and other members of the treatment team maintain responsibility for ensuring their patients are monitored for AEs of therapy.³⁶ Reporting and management of symptoms should continue to be part of routine care as more patients receive OC instead of, or in addition to, IV therapies.³⁶ In some cases, collaborative practice agreements empower pharmacists to direct some of the drug management by ordering labs and medications to manage certain anticipated AEs.³⁶ Some institutions utilize electronic monitoring, which can track medication and dose, AEs, and follow-up information. In some instances, these resources allow sharing of information between multidisciplinary providers such as nurses and pharmacists.³⁵

Patient adherence is an important factor in determining appropriate candidates for OC because much of the responsibility for dose and toxicity monitoring shifts to the patient in these cases.³⁷ It is important that these patients will not only take their medication at the doses and intervals prescribed but will also keep scheduled follow-up appointments and alert health care providers if they have any AEs related to therapy.³⁷ Patients should be educated on the correct dose and frequency of their medication, AEs to expect, and the importance of reporting AEs to their providers as soon as possible.³⁷

Many factors can contribute to nonadherence with OC, such as poor health literacy, limited patient education, complicated drug schedules, significant AEs, and significant out-of-pocket expense. These issues should be addressed prior to prescribing OC and should be continually evaluated throughout treatment to ensure patient adherence and successful treatment.³⁶

OC BEST PRACTICES: PRESCRIBING

At the time of prescribing OC, providers should educate patients about their treatment, covering topics such as expected outcomes, AEs, medication cost and access, medication administration instructions,

and monitoring requirements.³⁶ Providers should also assess patients for factors that may affect their adherence to medication.³⁸

Cost of OC can negatively affect patient adherence because OC medications are typically covered under prescription insurance plans as opposed to IV infusions, which are covered by medical plans.³⁸ According to one stakeholder, before prescribing, providers should make “a determination of the unique financial implications for the patient, depending on whether an oral or an IV is given. If it’s done on [Medicare] part B, it’s a certain way, and if it’s done on [Medicare] part D, it’s a certain way; the thing that’s missing here is a financial analysis of the impact to the patient.”

Patients may be more likely to delay treatment, delay refills, or take a lower dose of their OC to save money.³⁸ One stakeholder added, “[A] big challenge is cost for the patient. The cost to the patient out of pocket for an oral therapy can be very different than the cost to a patient for an IV therapy. The challenge is that there’s only so much that they can offer on the government payer side, and we rely heavily upon grants for some of those patients. You can initiate therapy, and then grant funding runs out before the end of the year. The patient is then in a really bad spot when grant funding is no longer available, and the drug manufacturer has limited ability to intervene on behalf of patients when it’s a government payer.”

Patients lacking adequate social support also have an increased likelihood of nonadherence to OC because they do not have assistance with receiving and retaining medication education, reporting AEs, remembering medication doses and appointments, and getting to appointments.³⁸ AEs also negatively affect adherence, with as many as one-third of patients discontinuing OC for this reason.³⁸

Patients receiving OC instead of IV may also be less likely to prioritize follow-up appointments.³⁸ Those with comorbidities are also at risk for OC nonadherence due to the potential for drug-drug interactions or direct effects of the medication on already-compromised organ systems.³⁸ Patients’ understanding of the disease and their attitude play a role in their treatment preference and ability to manage the disease.³⁸ “For us, patient preference is something that’s integral in the clinician’s practice, but on the health plan side, it usually starts with what the physician and the patient deemed to be most appropriate; it’s driven by the practice, not by the health plan,” according to one stakeholder.

OC BEST PRACTICES: EDUCATION

Patient education regarding expectations, AEs, cost, administration, and monitoring of OC is vital to assist patients in informed decision-making, as well as to improve medication adherence.³⁶ Education should be provided both verbally and in writing and at a level appropriate to each patient’s education level and preferences.³⁶ It is important that patients receive education prior to initiating therapy and continually during treatment.³⁶

Topics that should be covered during education include treatment-related issues, such as goals of treatment, as well as duration and schedule of treatment; known interactions with other drugs and

specific foods; information on AEs, including both frequent and rare events, potential effect on sexual function or fertility, and self-management techniques; what issues warrant immediate medical attention or advice; how to safely handle and dispense of medications; and follow-up expectations.³⁶

One stakeholder mentioned that “[we use] a patient calendar that we follow up with and more touchpoints, depending on the severity of therapy in the [adverse] effect profile.”

Ongoing patient education is one of the most important factors affecting medication adherence and, therefore, treatment success.³⁹ Frequent education allows providers to regularly reinforce the clinical reasons and the benefit of patients taking their OC medications as prescribed, thus improving adherence.³⁹

We use texting services that provide reminders to patients. It’s a bidirectional texting system, [so] you can ping the patient to say, ‘Did you have any [adverse] effects? Have you taken your medication today?’ And they can reply back to you.

OC BEST PRACTICES: DISPENSING

Regarding OC medication acquisition, patients should be screened prior to being prescribed OC to determine financial barriers to treatment and should be supported in navigating assistance programs and insurance requirements.³⁶ “We don’t really involve a preference of a formulary for [IV] oncolytics in most cases, but [regarding] oral [oncolytics, there can be] a drug access issue. Drug access is obviously a bit more complicated in the pharmacy benefit manager side, so we do sort of insert some formulary decision on that,” one stakeholder said.

Once an OC medication has been prescribed, it is imperative that a multidisciplinary team involving physicians, nurses, pharmacists, and other clinicians continue to monitor the patient for drug-drug interactions, need for continued patient education, proper drug distribution, patient access to the medication, AEs, and medication adherence.³⁶ One stakeholder added, “A lot of us now have a collaborative practice agreement, where [much] of the prescribing [is done by] the PharmDs that are working in the clinic. Many times, they’re the ones that integrate themselves in the specialty pharmacy.”

Patients should also be given information about the role of the specialty pharmacy and financial assistance, when applicable.³⁶

Pharmacists, along with the prescribing physician, are responsible for monitoring drug-drug interactions and AEs and alerting the care team and other entities (eg, the FDA) when they occur.³⁶ Pharmacists can also use methods such as prescription refill history, pill counts, monitoring of drug levels, and medication event records to communicate with the care team regarding ongoing patient adherence.³⁶ According to one stakeholder, “Access to the electronic medical record is a game changer for those [integrated delivery network]–owned specialty pharmacies. There’s just so much more integration at those sites. Again, I look at it as an extension of the treatment team.”

OC BEST PRACTICES: MONITORING

Any standardized medication-adherence assessment tool should be cost-effective, easy to use for the patient and provider, reliable, and practical.³⁶ A stakeholder mentioned one example of a simple intervention: “We use texting services that provide reminders to patients. It’s a bidirectional texting system, [so] you can ping the patient to say, ‘Did you have any [adverse] effects? Have you taken your medication today?’ And they can reply back to you.”

During follow-up visits, initial medication education should be reinforced, presence of symptoms or AEs should be assessed, and necessary interventions should be initiated.⁴⁰ Regular monitoring evaluations should also include an evaluation of new medications or therapies for assessment of drug-drug interactions and assessment of a patient’s ability to manage AEs.^{36,40}

Another stakeholder noted, “We’re piloting a new program using a technology texting function in our breast cancer patient populations. It is specifically related to diarrhea as an adverse effect, [and] it prompts the patient to respond via text regarding symptoms and diarrhea dehydration. It then grades the toxicity and triggers an in-basket message to the pharmacist for follow-up and early intervention for some [adverse] effects. Leveraging the [electronic health record] texting function for patient reported outcomes will, hopefully, [allow us to] intervene a little bit faster for patients with breast cancer.”

SUMMARY

Although mBC contributes significantly to morbidity and mortality in the United States, there has been much innovation in the field. Chemotherapeutic agents are continually being improved from both a toxicity and efficacy standpoint through the use of analogues, removal of additives, and formulation changes. As patients gain treatment autonomy and, thus, responsibility through oral therapies, special care and attention will be needed to ensure patient adherence to achieve optimal outcomes.

“[Are] there more real-time data so that you can see if somebody skipped a dose several times over a certain period of time and to what degree of it is tied to outcomes? How is adherence related to things like response rate and progression-free survival?” one stakeholder

asked. “[These are] all the things that we’re interested in, where adherence should drive better outcome[s].”

OC certainly has a role in the management of mBC, and many factors need to be considered and addressed to ensure successful treatment. •

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