The Use of Real-World Evidence for Oral Chemotherapies in Breast Cancer

KIROLLOS HANNA,[1] PharmD, BCPS, BCOP, and KELLEY MAYDEN,[2] MSN, FNP, AOCNP®

From [1]Mayo Clinic and M Health Fairview, Rochester, Minnesota; [2]Ballad Health Cancer Care-Bristol, Bristol, Tennessee

Authors' disclosures of conflicts of interest are found at the end of this article.

Correspondence to: Kirollos Hanna, PharmD, BCPS, BCOP, 200 First St. SW, Rochester, MN 55905. E-mail: kirollos11@gmail.com

https://doi.org/10.6004/jadpro.2021.12.2.12

Abstract

Almost all patients with breast cancer will eventually receive chemotherapy drugs, the majority of which are administered as IV infusions. Real-world evidence indicates that while current treatment paradigms vary considerably from guideline recommendations, there is an increasing trend towards a preference for oral oncolytics among patients with breast cancer. Recent data have shown that oral anticancer therapeutics represent 25% of the oncology drug market share and that there is a high demand for these agents. Therefore, oral formulations of chemotherapy agents such as paclitaxel are currently under development. Although oral oncolytics are associated with several advantages over conventional intravenous drugs, maintaining adherence to therapy is a major barrier in achieving improved outcomes with these agents. Advanced practitioners can facilitate improved adherence to oral oncolytics by integrating evidence into practice to support better education and communication strategies to address patient concerns, overcome key hurdles, and ultimately, empower patients.

There has been considerable progress in the treatment of breast cancer, and several targeted approaches have been integrated due to an improved understanding of the molecular basis of different subtypes (Waks & Winer, 2019). Ongoing research is focused on meeting the demand for novel drugs with better anticancer efficacy coupled with decreased adverse effects (Ades et al., 2017; Harris, 2018). Given the chronicity of breast cancer treatment, it is imperative to find agents that match the requirements of a long-term application conducive to enabling a high quality of life.

Currently, almost all patients with breast cancer will receive chemotherapy agents during their care continuum (Schneeweiss et al., 2015). However, conventional chemotherapy comprises complex IV regimens that necessitate frequent visits to medical centers (Hernandez-Aya & Ma, 2016). This adds a time and travel burden on patients and caregivers in addition to treatment-related toxicities and disease-related distress (Eek et al., 2016). Moreover, the placement of indwelling cath-

J Adv Pract Oncol 2021;12(2):13–20

eters for IV therapy is associated with fears and may lead to severe complications from infections. Consequently, cumbersome IV regimens are associated with patient dissatisfaction with treatment and nonadherence to therapy (Kallen et al., 2012). Therefore, it is not surprising that there has been an increased demand for oral anticancer agents, which now account for more than 25% of the oncology drug market (Weingart et al., 2008).

Capecitabine is an oral chemotherapy agent available for breast cancer treatment and is suggested for patients with bone-predominant, estrogen receptor–positive metastatic breast cancer (MBC) who have progressed on endocrine therapy (Hernandez-Aya & Ma, 2016). Other agents available for oral administration include cyclophosphamide, temozolamide, etoposide, topotecan, and methotrexate. Low bioavailability, however, has posed hurdles in the development of oral formulations for taxanes such as paclitaxel and docetaxel (Jibodh et al., 2013; Stuurman et al., 2013). Ongoing efforts are aimed at circumventing the issue of bioavailability and novel oral formulations of paclitaxel, and other commonly used chemotherapy agents are currently under development (Jibodh et al., 2013).

PATIENT PREFERENCE FOR ORAL THERAPIES

The oral mode of drug delivery is routine for most diseases and is attractive due to convenience and ease of administration for both patients and health-care providers (Eek et al., 2016). Oral agents also have the added benefit of improved quality of life and economic aspects, especially for patients and their caregivers (Stuurman et al., 2013). For example, oral agents do not involve traveling to and spending several hours in an infusion room, which is a major quality of life improvement. In addition, this eliminates expenditure on transportation, child care, and parking.

Several surveys and studies have reported an increased acceptance for oral drugs among patients and health-care professionals (Ciruelos et al., 2019; Eek et al., 2016; Navarro et al., 2002; Schott et al., 2011). An analysis of previous studies indicates that most patients who have experienced oral agents do not favor IV chemotherapy and report a clear preference for oral chemotherapy for breast cancer treatment (Eek et al., 2016). While some studies found a stronger preference for oral therapies among younger male patients as compared with older female patients, other studies were unable to establish age-related preference differences (Liu et al., 1997). For instance, Schott and colleagues (2011) reported that in a German breast cancer population, both older and younger age groups of patients were not concerned about incorrect use of oral therapies and expressed a medium-to-strong level of impact on daily life when compared with IV chemotherapy.

Recently, Ciruelos and colleagues (2019) have confirmed that a majority of patients (77%) with breast or lung cancer preferred oral therapy due to less disruption of daily life, no trouble in swallowing oral therapy, and no issues with missing doses. This patient population had already received IV therapy and at least two cycles of oral chemotherapy, with 56.3% reporting problems related to drug infusion with IV therapy, 61.7% expressing concerns about nurses failing to find suitable veins, and 63.1% reporting dissatisfaction with hospital waiting times (Ciruelos et al., 2019). In light of these data, an increasing number of oral chemotherapeutics are under development and are expected to become available soon (Jibodh et al., 2013; Stuurman et al., 2013). Recently, an oral formulation of paclitaxel and encequidar (improves bioavailablity) was associated with superior efficacy and tolerability in comparison with IV paclitaxel in MBC, and has been granted Priority Review by the U.S. Food & Drug Administration (Athenex, 2020).

CURRENT PRESCRIBING PATTERNS

The latest guidelines from the National Comprehensive Cancer Network (NCCN) suggest neoadjuvant, adjuvant, and subsequent therapy for patients with breast cancer based on subtype (NCCN, 2020). For example, endocrine therapy is the preferred choice for the first-line treatment of patients with hormone receptor–positive/human epidermal growth factor receptor 2 (HER2)-negative advanced and/or metastatic disease. In the event of resistance to endocrine therapy, these patients should be treated with single-agent chemotherapy. Similarly, for patients with triple-negative breast cancer, the guidelines suggest im-

munotherapy or single-agent chemotherapy and recommend reserving combination chemotherapy for patients with immediate life-threatening disease (NCCN, 2020).

In the real world, however, guidelines are not universally implemented; variations from guideline recommendations have been reported by several studies (Feinberg et al., 2019; Feinberg et al., 2020a; Gajra et al., 2020; Statler et al., 2019). A recent study has confirmed that among patients with MBC requiring palliative care, a majority did not receive guideline-concordant therapy, with many patients being administered combination chemotherapy as opposed to the recommended single-agent chemotherapeutics (Feinberg et al., 2020a). Interestingly, the most commonly prescribed single-agent chemotherapy in this study was capecitabine, which is the only oral single-agent therapy choice for MBC (Feinberg et al., 2020a).

In another study, Gajra and colleagues (2020) evaluated the prescribing and sequencing preferences for triple-negative MBC among US community oncologists and reported a deviation from current guidelines with respect to the use of atezolizumab with nanoparticle albumin-bound-paclitaxel (nab-paclitaxel) in programmed cell death ligand 1–negative patients and use of combination chemotherapy in the second and third line of treatment (Gajra et al., 2020). Guideline-discordant therapy was also reported among patients with hormone receptor-positive/HER2-negative MBC (Feinberg et al., 2020b). Of note in these studies was the rising frequency of capecitabine prescriptions, thereby providing real-world evidence of increasing use of oral therapies (Feinberg et al., 2020b; Feinberg et al., 2020c). Although taxanes, including paclitaxel, docetaxel, and nab-paclitaxel, are still the most frequently prescribed drugs as a class in real-world studies, a shift towards oral chemotherapy agents seems apparent (Feinberg et al., 2020a).

ADVANTAGES AND DISADVANTAGES OF ORAL THERAPY

Indeed, the shared decision-making approach is encouraged for breast cancer therapy that involves considerations for efficacy, tolerability, side effects, quality of life, adherence, and direct and indirect costs (Maes-Carballo et al., 2020). Therefore, advanced practitioners (APs) need to balance the advantages and limitations of oral anticancer therapies with those of recommended IV agents for the given patient scenario (Hicks et al., 2017). Table 1 shows patient-reported positive and negative attributes of oral and IV antineoplastic agents (Eek et al., 2016). As is evident from Table 1, patients with cancer seem to prefer oral oncolytics due to the convenience and ability to receive treatment at home, which translates into reduced number of hospital visits in comparison with IV treatment (Eek et al., 2016). This significantly impacts patient quality of life since it facilitates more time for enjoyable activities, increases family time, and reduces treatment-related work absences. There can also be a reduction in certain financial burdens such as costs related to transportation, parking, and child care, coupled with an increase in out-of-pocket costs (Hicks et al., 2017).

Conversely, when patients preferred IV therapy over oral anticancer therapy, the treatment duration schedule was the most frequently reported advantage (Eek et al., 2016).

Table 1. Patient-Reported Attributes of Oral vs. IV Cancer Therapy

Positive attributes of oral cancer therapy	Able to take at home, convenience, desire to continue working, no contraindications, previous issues with IV therapy, problems with IV access and needles, travel, place of treatment, efficacy, personal benefit, impact on daily life and relationships, coping, autonomy, side effects, mode of administration
Negative attributes of oral cancer therapy	Time required to stand upright, inability to eat or drink, forgetfulness
Positive attributes of IV chemotherapy	Efficacy, someone else can administer, experience with IV therapy, ability to treat illness, treatment schedule, less interference with daily activities
Negative attributes of IV chemotherapy	Side effects, negative impact on daily life

Note. Adapted from Eek et al. (2016).

Importantly, reduced efficacy or greater treatment toxicity were not favored by patients over convenience, and a preference for oral therapy was reported when the oral and IV formulations had equivalent efficacies (Eek et al., 2016). On the other hand, clinicians do not tend to have a strong preference for oral cancer therapies that stems from concerns with appropriate administration and ensuring adherence to complex treatment regimens (Eek et al., 2016). Moreover, clinicians and APs need to acknowledge that not all patients may be candidates for oral oncolytics, especially patients with mental health issues and cognitive dysfunction. Thus, although oral anticancer therapy has benefits in ease of administration, reducing staff time constraints, and shifting the responsibility of therapy administration on the patient, clinical practices need to be better equipped to determine eligibility of patients and maintain adherence to therapy (Hicks et al., 2017).

ADHERENCE TO ORAL ANTICANCER THERAPY

Conformity with treatment plans and complex medication schedules are integral to the successful implementation of oral oncolytics (Weingart et al., 2008). This would entail continual adherence to multiple daily doses and complicated administration instructions involving time and dietary restrictions (Eek et al., 2016). The challenges associated with putting the onus on the patient for self-management include ensuring patient safety and monitoring of adverse effects with less oversight and support (Weingart et al., 2008). Several studies have shown that patients tend to struggle with maintaining adherence to oral anticancer agents, with one study reporting a nonadherence rate of 37% (Greer et al., 2016; Hicks et al., 2017). While a study from 2002 reported a 16% adherence rate for oral oncolytics as compared with IV infusions, adherence rates as high as 52% to 100% have also been associated with oral anticancer therapy (Greer et al., 2016; Mathes et al., 2014; Puts et al., 2014).

Indeed, the repercussions of nonadherence to oral anticancer agents can be huge and highly impactful in terms of patient outcomes. Lower adherence to oral oncolytic therapy is known to correlate with shorter time to disease recurrence, worse quality of life, increased medical costs, and increased mortality (Makubate et al., 2013; McCowan et al., 2013). On the other hand, higher adherence to oral antineoplastic agents in breast cancer was associated with better patient outcomes (Hershman et al., 2011; McCowan et al., 2013).

Patient-centered communication and education are key to facilitating adherence to oral oncolytics (Greer et al., 2016). Patients need to be made aware of proper storage and handling instructions for oral antineoplastic medications in a clear and concise manner (Hicks et al., 2017). For instance, oral oncolytics should be stored in a safe place and away from children and pets. These medications need to be swallowed whole, and patients should use gloves or wash hands before and after touching them. Patients should also receive specific instructions for scheduling of all medications, including those for other comorbid conditions, and to address unexpected events such as vomiting or regurgitation of medications (Hicks et al., 2017).

Detailed education on common and rare adverse effects of anticancer drugs needs to be communicated to both younger and older patients as well as their caregivers (Hicks et al., 2017). These include hand-foot syndrome, severe rashes, anemia, overall weakness, arthralgia, extremity edema, and fatigue. Older patients especially need to be made aware of adverse effects that require immediate medical attention such as an unexpected decline in physical function, cognition, balance, coordination, motor skills, or gait and effects on the neuromuscular system (Hicks et al., 2017).

BARRIERS TO ADHERENCE

The convenience and self-reliance advantages associated with oral oncolytics can partly lay the foundation for nonadherence to treatment (Eek et al., 2016; Greer et al., 2016). A systematic review analysis has shown that adherence to oral antineoplastic therapy declines significantly over time, with varied factors related to patients, disease, treatment, and provider/health-care system, influencing nonadherence (Greer et al., 2016). To that end, in a study conducted by Partridge and colleagues (2003), breast cancer patients treated with tamoxifen reported 87% adherence rates in the first year of treatment, which lowered to 50% by the fourth year of treatment.

It is important to differentiate between unintentional and intentional nonadherence to identify and address underlying causes of lack of adherence (Hicks et al., 2017). Intentional nonadherence can occur when patients experience intolerable adverse effects, are unsure about the disadvantages of not adhering to treatment, are uncertain about the benefits of treatment, or are in denial over the need for treatment. In contrast, patients who simply forget to take their medications or missed medications due to a lack of understanding of the regimens demonstrate unintentional nonadherence.

Both intentional and unintentional nonadherence can be a consequence of a lack of established protocols that support and educate patients in adhering to oral anticancer drugs (Hicks et al., 2017). For example, patients need to have a clear understanding of their day-to-day regimen and should be prescribed therapy that meets their expectations and does not interfere with other medications that they are taking. Patients should be involved in the decision-making process and should be able to communicate their negative experiences with ongoing treatment. Detailed patient monitoring plans that document office visit frequency, laboratory visits to monitor response markers, and scheduled phone calls from providers' offices need to be integrated to evaluate adherence and encourage commitment to therapy (Greer et al., 2016).

Socioeconomic factors, such as cost, access, financial support, and social support, are also known to affect nonadherence to oral antineoplastic agents (Hicks et al., 2017; Navarro et al., 2002). Since oral oncolytics may have higher out-of-pocket costs and copayments, patients facing an increasing financial burden from their disease due to lost income and indirect costs may opt out of cancer therapy (Zafar et al., 2013). Some patients have reported debt, bankruptcy, cutting back on drug doses and groceries, and utilizing less heat in their homes in order to make payments for cancer therapy (Covinsky et al., 1994). Estimates have indicated that most patients with cancer end up paying $24,000 to $36,000 annually as out-of-pocket expenses in addition to higher insurance premiums. Such huge financial burdens, or in other words, financial toxicity, may dissuade patients from continuing with oral oncolytic therapy (Egerton, 2016; Zafar et al., 2013). Indeed, as compared with commercially insured patients, the rate of nonadherence to oral oncolytics is twice as much among Medicare beneficiaries due to high copayments (Tangka et al., 2010). Lack of timely access to oral anticancer drugs due to the need for a prior authorization and other time-consuming insurance formulary stipulations can further pose hurdles towards adherence (Hicks et al., 2017).

Lastly, just like patients with chronic diseases, limited social support and depression symptoms are known to negatively affect adherence to oral antineoplastic treatment (Greer et al., 2016).

THE AP'S ROLE IN IMPROVING ORAL ADHERENCE

Improving adherence to oral anticancer therapy represents a unique challenge for clinical practice. Before providing the option of oral oncolytics to patients with breast cancer, APs need to consider individual patient factors such as a complete medical history, physical and medical assessments, and whether the patient has the necessary support and motivation for adherence (Hicks et al., 2017). After collaborative discussions with patients about using the oral route for anticancer drug delivery, the multidisciplinary health-care team should ideally choose regimens or agents that are associated with less severe adverse effects such as neuropathy and cardiotoxicity (Hicks et al., 2017).

A key criterion for the choice of agents is a complete list of prescribed and over the counter medications that the patient is taking to reduce the risk of drug-drug interactions. Advanced practitioners need to ascertain that patients and caregivers are educated on the details and timings of the treatment regimen and recognize the importance of adherence to their regimen (Hicks et al., 2017). Patients need to be well-prepared for managing any expected or unexpected adverse effects and should be provided education on careful monitoring for timely identification of side effects or lack of response. Advanced practitioners need to assess patient and caregiver expectations and preferences and be ready to address any concerns during therapy (Hicks et al., 2017). Advanced practitioners can ensure that patients have timely access to their medications by collaborating with

specialty pharmacies that also have a successful compliance and adherence program (Osborne, 2019). Advanced practitioners could also inform patients about assistance and/or copayment programs established by pharmaceutical companies or the Patient Access Network Foundation for Medicare patients (Navarro et al., 2002).

Advanced practitioners need to be vigilant about identifying causes for nonadherence to suggest strategies such as calendars, electronic pill boxes, medication reminder apps, and patient financial assistance programs (Hicks et al., 2017; Ruddy et al., 2009). Motivational interviewing and behavioral coaching are known to aid APs in promoting adherence among patients reporting negative experiences with oral oncolytic therapy (Hicks et al., 2017; Ratliff, 2016). Use of new technology and telemedicine can be harnessed to promote safe administration and handling of medications while monitoring daily symptoms and adherence to oral antineoplastic drugs (Bingham et al. 2020; Greer et al., 2016). Smartphone mobile applications could be used to not only include personalized treatment plans but also to provide behavioral strategies to cope with adverse effects, and real-time reports on symptoms and medication adherence (Greer et al., 2016). Indeed, enhancing education and communication with patients taking oral oncolytics using telemedicine and novel technology platforms would be of immense value for APs to enable improved adherence (Ruddy et al., 2009).

CONCLUDING REMARKS

There is a growing demand for oral oncolytic therapy and oral formulations of commonly used intravenous chemotherapy drugs are under clinical development. Patients, however, are known to struggle with maintaining adherence to oral oncolytic agents due to complex regimens, adverse effects, costs, and lack of financial and social support. Advanced practitioners are well-positioned to mitigate these issues with improved education/communication strategies and novel technologies.

Acknowledgment

Writing assistance was provided by Nirupama Mulherkar, PhD (NM-INK, LLC), whose work was funded by Athenex, Inc.

Disclosure

Dr. Hanna has served as a consultant for AbbVie and Seattle Genetics, on advisory boards for AstraZeneca, Heron Therapeutics, Incyte, Rigel, Sandoz, Taiho Oncology, on the speakers bureaus for AbbVie, Astellas, BeiGene, Bristol Myers Squibb, and Seattle Genetics, and holds stock in CVS Health. Ms. Mayden has served on the speakers bureaus for Amgen, Pfizer, and Puma, and as a consultant for Amgen.

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