Oral Agents for Cancer: Safety Challenges and Recommendations

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Background: The lack of knowledge and standardization of safety practices related to prescribing, dispensing, administering, and monitoring oral agents for cancer (OACs) has created significant safety challenges for patients and healthcare providers. Problems identified with the use of OACs include possible medication errors, increased potential for toxicity, unintentional exposure of hazardous medications to healthcare providers and informal caregivers, and possible pollution of the environment.

Objectives: The purpose of this review is to provide information about the current state of knowledge and recommendations in the literature regarding safety concerns with OACs and strategies for risk reduction.

Methods: Articles published from 2003–2014 were retrieved using PubMed, CINAHL®, and the Cochrane Library.

Findings: As the number of OACs continues to increase, existing standards related to medication errors and safety will require ongoing revision to lessen the risks and hazards for patients, caregivers, and healthcare providers.

The use of oral agents for cancer (OACs) requires patients and families to self-manage medications that have a narrow therapeutic window and the potential for adverse effects in the community setting (Moody & Jackowski, 2010). OACs have many benefits for patients, including ease of administration, needleless administration, the body’s continuous and prolonged exposure to chemotherapy, and improvement in quality of life (Bartel, 2007; Birner, 2003; Trovato & Tuttle, 2014). However, these benefits are accompanied by risks. Because OACs are self-administered, the responsibility of the “five rights” (i.e., right medication, right dose, right time, right route, and right patient) shifts from nurses to patients and caregivers (Roop & Wu, 2014). Problems identified with this shift in responsibility include a possible rise in medication errors; increased potential for toxicity; unintentional exposure of hazardous medications to family, friends, and pets; and possible pollution of water supply and landfills (Bartel, 2007; Roop & Wu, 2014).

Patients typically feel a false sense of safety regarding OACs. In a study by Held, Ryan, Champion, August, and Radhi (2013) involving 50 patients, 40% reported that they felt OACs were safer than treatments administered via IV. Patients often believe that OACs are not as toxic or potent as IV therapy (Roop & Wu, 2014). Trovato and Tuttle (2014) also documented this perception and found that 79% of 45 patients surveyed said they believed OACs were very safe. Although these studies have limitations, this false impression of safety is well documented, indicating that patients may not understand the seriousness of the medication (Held et al., 2013; Trovato & Tuttle, 2014).

Safe handling of parenteral chemotherapy has been a topic of interest since 1985, when the American Society of Health-System Pharmacists first provided guidelines for the handling of hazardous drugs (Held et al., 2013). In the past decade, various organizations, including the American Society of Clinical Oncology (ASCO), National Institute for Occupational Safety and Health (NIOSH), Occupational Safety and Health Administration, and Oncology Nursing Society (ONS), have offered professional standards and guidelines to address the prescription, preparation, and administration of antineoplastic agents. These standards only marginally address the use of OACs (Neuss et al., 2013).
In December 2011, ASCO and ONS led a multistakeholder workgroup to review issues associated with the safe administration of OACs. The resulting document from ASCO and ONS (Neuss et al., 2013) provided new recommendations regarding important aspects of OAC administration, including prescribing, disposal, patient education, and continuity of managing medications across various healthcare settings. Past experience with the implementation of IV chemotherapy safety standards suggested that compliance with chemotherapy drug administration by healthcare providers is achieved incrementally in an ongoing process of improvement (Gilmore, Schulmeister, & Jacobson, 2013).

Hazardous drugs can pose significant health risks to healthcare workers and caregivers who are exposed to them (NIOSH, 2004). NIOSH defines a hazardous drug as one that may cause cancer, fetal malformations, adverse reproductive effects, organ toxicity, or genotoxicity (NIOSH, 2004). Much of what is known about the principles of safe handling of hazardous drugs came from studying injectable medications administered in a hospital or clinic (Jacobson et al., 2012; Roop & Wu, 2014). Although many factors of OAC treatment may appeal to patients and caregivers, the related, potentially serious safety issues deserve additional research to provide guidelines and evidence-based standards for clinical practice and community safety.

Medication Errors

Preventing medication errors is a priority of healthcare providers. Safeguards to prevent medication errors in patients receiving OACs present new and evolving challenges. Current literature does not provide data about oral versus IV chemotherapy administration errors (Goodin et al., 2011). However, OAC administration concerns include incorrect dosing and limited monitoring, which can result in under- or overdosing, serious side effects, morbidity, and mortality (National Patient Safety Agency, 2008). Bartel (2007) reported that 24% of cancer centers surveyed described a serious adverse event related to OAC therapy, and 31% described a serious near miss during the previous year.

Weingart et al. (2010) reviewed reports of OAC medical errors from a variety of sources, including medical literature, the Internet, and medication reporting systems, in addition to incident reports from 14 comprehensive cancer centers. The authors discovered that the most common medication errors involved the wrong dose (Weingart et al., 2010). However, the wrong drug being dispensed or the wrong number of doses or days being dispensed led to the most adverse events (Weingart et al., 2010).

The Institute for Safe Medication Practices (ISMP) highlighted in its medication safety alert newsletter a lomustine overdose that caused the death of a patient with brain cancer who, not realizing that a three-month supply of her medication had been dispensed in one bottle, accidentally took all of it at once (ISMP, 2014). The patient had previously received a one-month supply of medication from a mail-order pharmacy. In addition, this article highlighted five similar errors with the same oral agent, demonstrating the importance of medication counseling and clearly written patient instructions (ISMP, 2014).

Temozolomide, like lomustine, is a drug that has a high potential for error because of the different capsules and strengths needed to achieve a desired dose. Dose changes can make administration more confusing and a safety issue (Birner, 2003). If patients experience cognitive impairment, it may “affect their ability to understand instructions and prepare daily doses comprised of pills of various strengths” (Weingart et al., 2011, p. 4).

Medication errors can occur at many points along the prescribing, dispensing, and administration continuum (Bartel, 2007; Griffin, 2003; Neuss et al., 2013). For example, standard order forms are not consistently used for prescribing OACs (Goodin et al., 2011; Weingart et al., 2007). The literature suggests that safe prescribing should be done via an electronic order or prescription templates if an electronic system is not available (Bartel, 2007). Roop and Wu (2014) advised that all prescribing practices should have policies and procedures to guide effective communication with patients and families.

As more OACs become available, healthcare institutions are challenged to develop the appropriate safety support systems (Weingart et al., 2010). Less than 20% of cancer centers are set up to safely handle the administration and monitoring of OACs (Weingart et al., 2010). The sophisticated infrastructure implemented for the administration of parenteral chemotherapy, including electronic order entry with decision support and clinician double-checks, is not as robust for OACs (Weingart et al., 2008). Safety measures, such as a double-check for OACs, do not appear to be common practice (Weingart et al., 2010).

Improvements can be made in the area of regimen complexity. Simplification or standardization of the regimens could help to decrease errors. Weingart et al. (2010) suggested that pharmaceutical companies and manufacturers create clinical trials and dose forms to simplify prescribing, dispensing, and administering. Clinicians need to thoroughly review orders with patients, double- and triple-checking that the correct dose, days, and drug are dispensed to the patient. Nurses can follow up with patients to confirm that they know what, how, and why they are taking their OACs (Weingart et al., 2010).

Financial Concerns

Financial issues can affect patients’ ability to adhere to the prescribed medication regimen, which is a safety concern. The expense of OACs is significant and can cost thousands of dollars per treatment cycle (Birner, 2003). The use of OACs may cost more than parenteral treatment, particularly when deductibles and inadequate insurance coverage exist. Patients may decide not to fill their prescription or may take their OACs intermittently, which can lead to treatment failure (Bartel, 2007). Because of the narrow therapeutic window of OACs, underdosing may affect disease survival (Bartel, 2007). Nurses have stated that OACs are prohibitively expensive; some applications for financial assistance are as difficult to complete as those required when applying for a scholarship or a mortgage (Roop & Wu, 2014). Many patients face an ethical dilemma when deciding how to pay for their OACs and often deplete their savings to pay for life-saving treatments (Roop & Wu, 2014).

Prescribing

Institutional requirements for the prescribing of OACs vary and generally are not as structured in the community setting.
(Birner, 2003). Reeves, Kam, and Storey (2013) reported that most (98%) of the 123 institutions responding to their survey allowed oncologists to prescribe OACs, and 42% allowed all attending physicians to order the treatment. Simmons (2010) stressed that oncologists or specially trained practitioners should order OACs. Practice policies and guidelines that specify practitioners’ qualifications and ongoing continuing education needs can provide additional organizational oversight (Neuss et al., 2013).

National data regarding the prescribing and subsequent management of patients receiving OACs in the outpatient setting are not available. The literature suggests that prescribing safety is enhanced with computerized order entry or prescription templates to provide additional clinical guidance and checks (Bartel, 2007; Weingart et al., 2012). One study described a prescription-writing module in an outpatient electronic medical record and suggested that decreasing prescription free-text areas (i.e., nonstandardized areas that require more keystrokes and may result in errors) would help to improve prescriber satisfaction and result in increased safety of the order (Weingart et al., 2012). The literature notes that OACs should be prescribed using prescription formats similar to parenteral chemotherapy, with vital information (e.g., height, weight, calculated body surface area, age, laboratory values, cancer diagnosis, treatment intent) and clear instructions for dosage, frequency, and administration (Lester, 2012; Weingart et al., 2012).

In a national online survey, only 56% of the nurses responding reported that their facility had a reliable communication system to provide notification when a patient received a prescription for OACs (Roop & Wu, 2014). Communication of the OAC plan to the interdisciplinary team is crucial to ensure adequate patient education and follow-up, which affects patient safety (Weingart et al., 2008). Consequently, developing communication protocols to make sure that patients and caregivers are properly educated to monitor and report side effects and toxicities in real time is crucial to safe management of OACs in the home setting (Moody & Jackowski, 2010; Weingart et al., 2008).

Dispensing

OACs are dispensed to patients in multiple venues, including specialty, community, national, local, private, mail-order, hospital, and office-based pharmacies (Weingart et al., 2008). Outpatient pharmacists most frequently do not have all of the patient information and parameters that are available to pharmacists dispensing IV chemotherapy in an institutional setting (Birner, 2003). In addition, once OACs are dispensed, patients will manage them remotely, including assuming the responsibility for contacting a healthcare provider with questions or issues that arise as a result of self-management (Bartel, 2007; Lester, 2012; Weingart et al., 2008). Each of the distribution routes has unique implications for the patient, prescriber, and dispenser (Weingart et al., 2008).

Mail-order pharmacies usually provide a 90-day supply of medication. This can result in decreased opportunities for patients and caregivers to interact with a pharmacist or healthcare provider, affecting the safety of OAC handling and administration (Weingart et al., 2011). Specialty pharmacies have been able to successfully address some of the limitations of mail-order pharmacies by providing expertise for a specific class of therapeutic drugs, such as OACs; however, patients receiving drugs for comorbid conditions may receive medications and education from multiple sources, resulting in confusion and conflicting instructions (Weingart et al., 2008).

Hospital and community pharmacies have varying levels of expertise. Cancer centers have oncology-trained pharmacists and nurses who review medications and interact with patients; however, almost half of OAC prescriptions are filled outside of the system (Weingart et al., 2008). The community pharmacy dispensing OACs may lack the expertise to provide counseling and education related to specialty medication. Although most pharmacy chains require documentation of medication education, the quality and value varies considerably (Weingart et al., 2008).

No documented competency requirements exist for individuals who dispense or administer OACs (Goodin et al., 2011; Neuss et al., 2013). The literature recommends that healthcare providers who prescribe, administer, or educate patients treated with OACs participate in a comprehensive education program that includes material regarding the safe handling of hazardous medications and toxicities of complex regimens (Goodin et al., 2011; Lester, 2012; Neuss et al., 2013).

Administration

Before starting OACs, patients should be able to physically ingest and absorb the drug (Birner, 2003). Ensuring that patients understand how to take the prescribed OACs and when to call their healthcare providers is critical to the safety and success of the treatment plan. To maximize the benefit of the treatment and decrease potential safety hazards, patients and caregivers require careful instructions related to OAC administration (see Figure 1). In addition, nurses should assess patients’ understanding of the instructions they received using the “teach-back” method, which involves asking patients to describe in their own words what they have learned after the information is presented (Griffin, 2005).

In the healthcare setting, a double-check of OACs should be completed by two oncology nurses prior to administration.
(Weingart et al., 2011). When OACs are administered in a non-traditional healthcare setting (e.g., assisted living facility), the literature advocates that the nurse double-check with the patient, family member, pharmacist, or other assisted living personnel (Griffin, 2003).

Follow-Up and Monitoring

OACs have many known and unknown risks of toxicity (Ni raula et al., 2012). Niraula et al. (2012) noted that “most newly approved anticancer drugs are associated with increased odds of toxic death, treatment discontinuation, and severe adverse effects compared with the standard treatment received by the controls” (p. 3,017). One safety concern related to the self-administration of OACs is patients’ self-management of drug toxicities that may require a reduction or discontinuation of treatment. Patients may suffer silently, fearing that disease progression is worse than the negative and possibly life-threatening effects they are enduring (Lester, 2012; Roo & Wu, 2014). Because patients are not seen by a healthcare provider with each administration, the potential for missed communication is a real concern. A standard approach to patient toxicity monitoring and symptom management is key to safe management of OACs.

Patients should be advised to inform all of their care providers that they have taken or are taking OACs for treatment of a cancer diagnosis. Providers can then be alerted to any potential toxicities and possible interactions with other medications or treatments prescribed. They must also wear the appropriate personal protective equipment when handling patients’ body fluids.

Safe Handling and Storage

Patients and Caregivers

Educating patients and caregivers to prevent unintentional exposure and contamination is essential. Studies have shown that over time and with repeated exposures, small amounts of hazardous drugs can cause negative effects (Simmons, 2010). A decrease in adverse effects and exposure has resulted from increasing awareness and proper safeguards (Simmons, 2010). The literature shows that patients and caregivers may not real-

ize the importance of proper handling, storage, or preparation of OACs (Held et al., 2013; Trovato & Tuttle, 2014). Patients have reported that they are not consistent with hand washing after handling OACs (Held et al., 2013; Trovato & Tuttle, 2014). In addition, the literature notes that caregivers may not have worn gloves, pregnant women may have handled toxic medications, and families may have saved unused medication for use in future cycles or disposed of it in the trash, sink, or toilet (Held et al., 2013; Trovato & Tuttle, 2014). Held et al. (2013) also reported that patients and their caregivers have used the same equipment to prepare or store their OACs and their nonchemotherapy agents. Patients and caregivers may require education with frequent reinforcement regarding how to safely handle and store OACs in the home setting (see Figure 2).

When handling body fluids, clothes, and linens that have been exposed to body fluids, patients and caregivers should consider following safety precautions for as many as seven days, rather than 48 hours, after stopping OACs (Goodin et al., 2011; Griffin, 2003). For patients who take OACs continuously, the precautions may never stop. Goodin et al. (2011) explains,

These recommendations are supported by a recent publication involving cyclophosphamide exposure that showed significant contamination on and around the toilet and that the use of gloves reduced personal contamination from changing bed linens one-to-six fold. . . . [These] drugs are eliminated from the body as active or inactive metabolites in sweat, urine, saliva, or stool for five to seven half-lives. (p. 11)
To decrease inadvertent exposure to others, patients should be encouraged to flush the toilet with the lid down; in addition, male patients should sit to void.

Exposure to OACs during sexual activity is a difficult topic to discuss because evidence is not readily available or consistent. However, traces of OACs may exist in semen or vaginal fluid, so barrier contraceptives should be recommended (Polovich, Olsen, & LeFebvre, 2014). Patients should be educated that eating, hugging, and kissing are safe (Polovich et al., 2014).

Healthcare Providers and Manufacturers and Distributors

The same precautions that healthcare providers practice when handling hazardous parenteral drugs should be used when handling OACs. Healthcare agencies’ hazardous drug policies and procedures should include OACs and be consistent with professional and regulatory standards set by various organizations, such as ONS and NIOSH (Simmons, 2010). In addition, organizations should determine who at the facility can administer OACs if oncology-trained professionals are not available. Because of the hazardous nature of OACs, healthcare workers must protect themselves from inadvertent exposure. A number of specific approaches for safe handling by the healthcare provider can be found in the literature (see Figure 3).

Pregnant healthcare workers working in a chemotherapy setting can be controversial. The goal of limiting or removing the worker from any exposure to OACs is not always practical (Goodin et al., 2011). If nurses become pregnant or are trying to conceive, they may want to consider asking for another assignment; however, if patients being treated by chemotherapy by any route are the only type of patients they take care of, exposure to OACs will be difficult to avoid.

Safe handling of OACs is an issue that deserves the attention of manufacturers and distributors. Although the literature does not have many safety recommendations for manufacturers and distributors, a few precautions have been noted (see Figure 4).

Targeted Therapies

With many of the newer treatments being targeted OACs, the question of whether they need to be handled in the same way as other OACs often arises. These targeted OACs do not reach all rapidly growing cells like cytotoxic therapy; instead, they block specific pathways in the malignant cell (Reeves et al., 2013). These newer OACs do not cause collateral damage to healthy cells in the way that cytotoxic therapy does. Unfortunately, little documentation exists to support handling them in one way or another (Reeves et al., 2013). Until more data related to handling these types of OAC are available, many healthcare institutions are being conservative and continuing to treat them like other OACs.

Implications for Practice

- Develop relevant policies and standard operating procedures regarding the reduction of safety concerns related to the use of oral agents for cancer (OACs).
- Educate patients, informal caregivers, and other healthcare providers about various issues related to OACs, as well as strategies for risk reduction.
- Have mechanisms in place for patient follow-up, access to providers in urgent situations, and effective symptom management.

Implications for Nursing and Conclusions

OACs are frequently believed to be a less toxic form of cancer treatment, and the lack of knowledge and standardization of safety practices specific to OACs has created significant safety challenges for patients and healthcare providers (Goodin et al., 2011; Moody & Jackowski, 2010; Simmons, 2010). Although OACs may be a convenient form of cancer treatment, patients, caregivers, and healthcare providers face exposure risks similar to those posed by IV chemotherapy (Goodin et al., 2011). With an increasing number of OACs coming on the market, previous standards related to medication errors and safety will require ongoing revision to reflect new risks and hazards for the patient, caregiver, and healthcare provider (Bartel, 2007; Neuss et al., 2013; Weingart et al., 2012).

This article provides information about the current state of knowledge regarding safety issues and concerns with OACs, as well as recommendations in the literature concerning strategies for risk reduction. Nurses and others can use this information to develop relevant policies and standard operating procedures to address the issues identified. Suggested strategies in this article can be used to educate providers, patients, and informal caregivers about safe practices, patient knowledge needs, and the importance of toxicity identification, prevention, and management. Safety mechanisms should be in place for patient follow-up, and providers should be available for urgent situations, as well as for effective symptom management. As discussed elsewhere in this supplement, the nature of OACs and their reliance upon self-administration exposes problems in adherence as a safety issue. Addressing patient adherence is a crucial factor to promoting safety and effective disease treatment.

FIGURE 4. Suggested Precautions for OACs for Manufacturers and Distributors

Note: Based on information from Goodin et al., 2011; Griffin, 2003; Lester, 2012; Simmons, 2010.

- Package OACs effectively, and segregate from other medications.
- Store and transport OACs separately from other medications.
- Label package as cytotoxic, as applicable.
- Create durable, tamper-proof packaging with a one-time or limited-time use.
- Produce liquid formulations for easy and safe compounding of OACs.
- Provide safe handling information to the end users, including transportation, compounding, and administration.
- Maintain current patient education information.
OAC—oral agent for cancer
References


