

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Barriers to Adherence to Oral Drug Regimens in Oncology and Strategies for Improvement



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H&O How common are oral drugs in oncology?

JB Approximately 25% to 35% of the drugs currently used in oncology are administered orally. Most of the small-molecule drugs in development are administered via an oral route.

H&O What are the advantages and disadvantages of oral administration?

JB An advantage of oral administration is that patients can take the drugs themselves, on their own, in their own home. They do not have to visit a clinic, which eliminates any logistical issues related to scheduling or travel, as well as time spent waiting for an infusion. Oral agents allow patients more autonomy. Theoretically, the tolerability of oral drugs should also be a little better, although this is not necessarily true in all cases.

Although some oral agents for the treatment of cancer are cytotoxic (eg, busulfan, capecitabine, and melphalan), the large majority are “targeted” agents that block tumor cell proliferation via a targeted mechanism. A disadvantage to oral therapies is that pharmacokinetic properties often lead to a short half-life that requires daily administration. Depending on the mechanism of action and the toxicity of the agent, the regimen or dosing schedule may vary. For example, some oral agents might be administered every day, and some may be administered every other day or with a week off in each cycle. For the most part, however, patients treated with oral agents are required to think about the drug daily. Intravenous or subcutaneous therapies are administered less frequently, and once weekly, once monthly, or once every 2 to 3

weeks are common regimens. Therefore, for intravenous or subcutaneous therapies, the patient does not have to focus on treatment every day.

There are other disadvantages of oral agents concerning access and cost. Health insurance companies, as well as Medicare and Medicaid, have different reimbursement schedules for drugs that are administered in a hospital or clinic vs those that are administered at home. Patients often have to pay more for oral drugs. Oral therapies are often covered under a prescription benefit, which tends to require higher copayments than the medical benefits that would cover therapies administered in a hospital or infusion clinic. In addition, most oral drugs must be shipped from a specialty pharmacy; they cannot be picked up at any local drugstore. There may be additional fees added by the specialty pharmacy. Another hurdle is that many pharmacy benefit managers, which decide which drugs will be covered under a patient’s prescription benefit, require prior authorization for oral medications for the treatment of cancer. The prior authorization process is burdensome not only for the patient but for the healthcare system in general, and can require multiple phone calls on behalf of the pharmacy and the treating oncologist in order to get an oral treatment approved and covered for the patient.

The concept of oral anticancer treatments sounds great, but these agents might not be the panacea patients were hoping for.

H&O What are some ways clinicians can measure adherence to oral drugs?

JB Patients often want to please their doctors, therefore, an outright question about adherence might fail to elicit

the truth. An alternative would be to start with a question such as, “How does taking the drug every day make you feel?” Further questions could explore whether the drug has negative or positive connotations for the patient. The patient might report adverse events. If the patient mentions any negative experiences with the drug, follow-up questions can explore what they do to address them. For example, the clinician can ask, “Do you skip your next dose?” or “Are you still taking the drug every day even though you feel this way?” These types of questions might allow patients to feel more comfortable discussing their adherence to the treatment regimen.

Clinicians can also check on whether the patient is obtaining refills on time.

Ideally, a drug should be approved with the most flexible dosing regimens and administration conditions possible.

H&O What are some barriers to adherence to oral drugs?

JB Cost is a barrier. Some patients may have limited financial resources or trouble with obtaining reimbursement from an insurance company to cover prescription refills. To extend the treatment duration, these patients might split the tablets or take the drug less frequently than prescribed (eg, every other day rather than every day).

Toxicity is another barrier to adherence. For example, if the drug causes diarrhea, a patient might skip the dose on a certain day in order to spend time away from home. There are several quality-of-life adverse events that are likely to impact adherence, such as fatigue, nausea, vomiting, and diarrhea. Even toxicities that are considered to be a relatively low grade of severity (\leq grade 2) can be highly distracting to a patient if they occur every day. Adherence might become poor in these situations, especially if the patient needs to leave home and/or requires energy for other activities.

Another barrier to adherence to oral therapy can be restrictive dosing requirements. For example, some drugs must be taken with a meal, and others should be taken in a fasting state. To avoid drug-drug interactions, some comedications must be avoided entirely or the treatments

must be spaced apart. Adherence might be impacted if a patient forgets to follow this schedule. For example, a drug might need to be taken before breakfast in a fasting state. If the patient forgets one day and eats breakfast before taking the drug, he or she might skip the dose for that day. It can be helpful to inform the patient when there is some flexibility with the dosing. In the previous example, it might be possible to take the drug before lunch. Clinical trial data exploring such label restrictions could provide insight into whether they are in fact needed, and thereby help improve adherence.

H&O What are the potential risks of inadequate adherence to oral drugs?

JB A patient who does not take their therapy as directed may fail to reach the therapeutic drug level that will lead to full benefit. The main risk is that the lack of efficacy will allow the cancer to recur and/or metastasize.

H&O Are there any patient characteristics associated with decreased adherence?

JB Even the most diligent and rule-abiding patients can falter in the face of toxicity or strict regimen requirements. Patients without a stable home or care situation might be less adherent to treatment.

H&O What are some strategies to improve oral drug adherence?

JB The best strategy would be to optimize the dosing strategy by simplifying the schedule and minimizing adverse events. This optimization should be done before the drug undergoes evaluation for approval by the US Food and Drug Administration (FDA). Most oral targeted drugs are not dose optimized. The initial starting dose is typically high, and then titrated down if the patient develops toxicity. Starting treatment at a more tolerable dose that still provides efficacy but with fewer adverse events would increase overall adherence while maximizing efficacy. It would also be helpful for the sponsors that develop drugs to evaluate the effects of food, drug interactions, and different dosing regimens before the drug is approved by the FDA. Ideally, a drug should be approved with the most flexible dosing regimens and administration conditions possible.

It would also be helpful for clinicians to inform their patients of whether treatment-related toxicities are expected to be short-term or long-term. In some cases, a particular adverse event might abate after the patient builds up tolerance to therapy. It might be easier for patients to adhere to treatment if they know that a particular adverse

event will eventually subside. Frank conversations about what to expect can help patients adhere to treatment.

Disclosure

Dr Bullock is employed by Certara, a strategic drug development consulting firm, where she advises multiple biotech and pharmaceutical companies on drug development. Dr Bullock is a stock holder of Certara.

Suggested Readings

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