

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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Pack-Splitting to Improve Cost-Effectiveness of Oral Agents in Oncology



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H&O What is the rationale behind the investigation of alternative dosing strategies of oral agents in oncology?

RDH There are 2 key drivers of the rationale behind this movement. The first is the high costs of these medications to payers and, more importantly, to patients who must cover out-of-pocket costs. These strategies aim to maximize value to patients and payers to ensure that the overall system can continue to bear the costs of these drugs.

The second rationale is that many of the available oral agents require dose reductions in a variety of patients. Therefore, the approved doses may be wrong in many cases. Early-phase investigations establish a maximum tolerated dose for new molecular formulations of oral drugs. Subsequent registration trials sometimes show that a large proportion of patients require dose reduction at some point owing to tolerability issues or other adverse events.

H&O Are there any recent insights into the pharmacology of oral agents in oncology that would impact their dosing?

RDH There is an incomplete understanding of factors such as the effects of food on the absorption of medications. Researchers are not necessarily optimizing formulations of drugs in the pre-approval and post-approval spaces. For example, they may overlook the possibility of controlled-release formulations. Dosing strategies for oral agents should reflect not only the dose itself but also

whether the drug is taken with or without food, as well as any interactions with other drugs. With the newer oral agents, this information is less clear than it used to be.

H&O Could you please describe the pack-splitting strategy?

RDH Mark Ratain, MD, and I proposed the concept of pack-splitting in an editorial published in *JAMA Oncology*. The concept of pack-splitting refers to oral drugs that are distributed in packs within cartons. In many cases, pharmaceutical companies are moving toward charging a single price for monthly supplies of drugs packaged in dosing cards. The idea behind pack-splitting is to dispense a drug at a certain dose, and then instruct the patient to take a lower dose contained within the total dispensed strength(s). That way, the blister pack is extended for 3 to 4 times vs the standard dose. Some blister packs contain capsules with different strengths, such as 2 mg, 5 mg, and 10 mg, and patients can be instructed to take a lower dose. As another example, say a blister pack contains a total of 40 mg of a drug, in four 10-mg capsules, intended for treatment of a certain cancer. For another type of cancer treated with the same drug at a lower dosage, say 10 mg or 20 mg, the patient can be instructed to take one or two 10-mg capsules daily rather than the entire 40 mg.

H&O Which settings might benefit from a pack-splitting strategy?

RDH There are several circumstances in which a clinician might want to prescribe a lower dose of a drug

packaged for prescription at a higher dose. Clinical data may support the lower dose. It can also be helpful to extend the time between co-pays. An important point is that for some drugs, the cost is the same regardless of the dose.

H&O Are there research data to support the pack-splitting strategy?

RDH The research data have focused on drugs that are used at different doses for different cancers. For multiple drugs, tolerability varies across cancer populations. For example, patients with thyroid cancer can tolerate much higher doses of a drug than patients with hepatocellular carcinoma or liver cancer. In this example, a patient with hepatocellular carcinoma might be able to use the same blister pack as a patient with thyroid cancer, but would take a capsule every other day instead of every day. The strategy involves a combination of pharmacy packaging plus clinical pharmacokinetics.

H&O Are there any barriers to this practice?

RDH Practitioners may be hesitant to adopt this strategy based on fears that patients will take incorrect doses, specifically doses that are too high. However, we often instruct patients to take varying medication strengths and regimens in daily practice. Examples that are relevant to this discussion include altering warfarin dosing regimens, modifying capecitabine strengths, and prescribing lenalidomide (Revlimid, Celgene) for 2 of 3 weeks. The success of these strategies, in combination with the growing role of specialty pharmacists and counseling, should address these concerns. Other barriers mentioned include insurance and payor adoption concerns. This argument, however, confounds me. If patients and payors save money—and we can do this safely—what is the concern? Another voiced barrier is pharmacy law. However, state laws allow prescribers the flexibility to give specific directions on formulations and how patients should take medication, as long as the instructions are clear to all parties.

H&O What factors make a patient a stronger or weaker candidate for the pack-splitting strategy?

RDH To be a good candidate for this approach, the patient should be able to understand the revised instructions provided by the prescriber and the pharmacist. A weaker candidate would be a patient with some degree of cognitive dysfunction who is taking many medications. A nonstandard regimen might be more challenging for such a patient to follow.

H&O How can study designs incorporate evaluation of pack-splitting strategies?

RDH This strategy could be tested in a randomized trial in which one arm consists of the standard dose of a drug given in a blister pack and the other arm consists of the same blister pack, but with instructions to take a reduced dose. Endpoints could include treatment outcome and adverse events, as well as costs and overall expenditures for the patient and the health care system.

These strategies aim to maximize value to patients and payers to ensure that the overall system can continue to bear the costs of these drugs.

H&O Are there any other alternative dosing strategies under investigation?

RDH There are several proposed strategies. One would be pack splitting and regimen alterations with other medications. An example would be to assess the half-life of a drug given daily, and, when feasible, extend the interval to a longer period. Another is to de-escalate the dose following initiation. The dose would start at the labeled recommendation, and then would be reduced in cases where it is possible to maintain disease response. For certain treatments, the relationship between the amount of drug in the blood and the degree of cancer control is not clear. That is to say, outcome is the same in patients with a high drug level as in those with a low level. In this circumstance, a clinician might consider starting the drug at a higher dose and then deescalating over time, with the idea of maintaining response while reducing the dose. One example is with ibrutinib (Imbruvica, Pharmacy-clinics/Janssen), which was de-escalated from 420 mg daily to 140 mg daily over 3 months in a 2018 trial conducted at MD Anderson.

A strategy proposed for monoclonal antibodies, which are administered intravenously, is to extend the duration between treatments. This strategy would reduce the overall number of doses, thereby decreasing costs to the patient and the health care system.

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Another strategy for certain drugs is discontinuation. Some cancers are addicted to certain pathways. It might be possible to stop treatment in patients who maintain a deepened response after a certain period. Evolving data show that if the cancer returns, restarting the drug at the same dose will recapture the response.

Another approach is to change the amount of drug that reaches the blood by altering how it is given and/or what drugs are given concurrently. This strategy has been tested with abiraterone acetate (Zytiga, Janssen). I was an investigator in a study that evaluated absorption, biomarkers, and cancer response of abiraterone acetate at 2 dosing regimens: 1000 mg given on an empty stomach vs 250 mg given with food. The study found that the 2 regimens were equivalent. By giving one 250-mg tablet a day compared with 4 tablets, a bottle of 120 tablets lasts 4 months instead of 1 month. Another way to boost the amount of drug in the blood is through intentional interactions, where a drug is given at a lower dose in combination with a drug that inhibits metabolism, allowing for administration of lower doses. This strategy has been historically employed with cyclosporine and ketoconazole in patients who undergo a solid organ transplant, to save money on cyclosporine costs.

The pack-splitting approach is part of an overall strategy encompassing interventional pharmacoeconomics and clinical pharmacology. As part of this strategy, researchers are focusing on a drug's value in an effort to reduce cost to the patient and the health care system, while maintaining disease response. Data from pharmacology studies suggest that there are many opportunities

to meet this goal, and numerous tools are currently under investigation.

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Suggested Readings

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