ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Novel Approaches to Optimization of Drug Dosages

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H&O What does it mean to optimize drug dosage?

CM Drug dosage encompasses the volume of the drug taken at a particular time, how often the patient takes it, and how long the patient takes it. Optimizing the dosage means finding the best balance between efficacy and adverse events, while also taking cost into account. Cost refers to more than just financial cost; it also encompasses factors such as time spent going to the clinic office and receiving infusions.

H&O Why is dosage optimization important in oncology?

CM Of course, we care about getting the best results for the patient. In addition, the system should care about the cost, regardless of who is paying. Even if the patient has health insurance and is responsible only for copays and deductibles, someone is paying for the treatment.

H&O What are the limits of clinical trials when it comes to establishing drug dosages?

CM There are no inherent limits when it comes to clinical trials. One could, in principle, run all kinds of multi-arm clinical trials with different dosages and get a fine-grain comparison of the different dosages. That does not happen in practice, though. When pharmaceutical companies are funding phase 3 trials of cancer drugs with the goal of US Food and Drug Administration (FDA) approval, it is rare to have any comparison of different dosages. The norm for cancer drugs is to determine the maximum tolerated dose (MTD) in phase 2 dose-finding trials and then compare the MTD with a placebo or the standard of care. We just do not see comparisons of different dosages.

Phase 2 dose-finding trials have the potential to be useful as a source of evidence, but there are 2 impediments to this happening. First, the sample sizes tend to be small. Second, the results are often used by pharmaceutical companies but not published. As a result, we learn much less about variation in dosage from existing clinical trials than we could in principle.

H&O How does the current system incentivize the approval of higher dosages than necessary?

CM Two problems are related to incentives: one on the health side and one on the financial side. On the health side, a longstanding practice in medicine is to prioritize the so-called primary outcome over various secondary outcomes. The primary outcome in a clinical trial of a cancer drug is always based on a measure of efficacy, such as disease-free progression or overall survival. The toxicities that lead to adverse events are considered secondary outcomes. The FDA drug approval process is based primarily on the primary outcome of efficacy, which incentivizes investigators to maximize that outcome with the highest dosage they can use of a drug—the MTD. The FDA also makes use of the statistical theory of hypothesis testing in evaluating drugs, which contributes to the approval of higher dosages because it is easier to pass the FDA test with a higher dose than with a lower one. I have been very critical of hypothesis testing in drug approval.[1] Both primary outcomes and hypothesis testing, as used by the FDA, promote higher-than-optimal drug dosages.

On the financial side, one does not need to be an econometrician like me to know that pharmaceutical firms have a financial incentive to dose as high as they can. They can earn more profit from a higher than from a lower dosage. So, there are both health and financial incentives to get dosages approved that are higher than they probably should be.

> I would like to see a far richer set of dosing trials than we have now.

H&O Have researchers been successful in obtaining direct data on reducing the dosage of certain agents?

CM On occasion. A good example is the drug trastuzumab, which is used for the adjuvant treatment of certain kinds of breast cancer. The original approval called for 12 months of use, but oncologists began to speculate that a lower dosage might be equally or almost equally as effective while reducing the risk of adverse events, especially cardiotoxicity. A lower dosage also reduces cost, of course. Several research groups in the United Kingdom carried out trials investigating a lower dosage. The best known of these is PERSEPHONE, a well-designed trial that compared 6- vs 12-month dosing of trastuzumab.[2] This trial showed not only that 6 months of treatment was noninferior to 12 months of treatment but also that the risk for cardiac events was significantly reduced with 6 months of treatment. Trials like PERSEPHONE should be done routinely, but they are rare.

H&O Is there a way for providers to obtain information about alternative dosages on the basis of existing data?

CM There is a way to obtain additional information from existing data, and this has been a focus of my own work. In a standard analysis of a clinical trial that compares lower and higher dosages of the same drug—call them treatment A and treatment B—we learn nothing about treatment B from treatment A, and vice versa. What I propose is that we take away additional information from these comparisons. If the efficacy and toxicity are higher with treatment B than with treatment A, it is reasonable to assume that they would be somewhere in between for a dosage that is in between. The research I have done has formalized how one can make use of that information by working it out mathematically. There is no way to get a precise estimate of patient outcomes at an intermediate dose, but one can do a sensitivity analysis that yields informative lower and upper bounds on what these outcomes will be. This research appeared online in *Epidemiology*.[3]

H&O What studies would you like to see conducted?

CM I would like to see a far richer set of dosing trials than we have now. The pharmaceutical firms do not have an incentive to conduct more of these, but the FDA could require pharmaceutical companies to provide more dosing evidence from phase 3 trials when they submit their new drug applications. The FDA could also require pharmaceutical companies to conduct post-marketing trials on dosing. Alternatively, the federal government or private foundations could fund such trials. We can also learn more from mathematical modeling, in vitro studies, and animal studies.

H&O Could you talk about your personal experience with cancer care?

CM I have a personal as well as a professional interest in cancer drugs because I was given a diagnosis of melanoma in 2012 and have since experienced 3 recurrences.[4] In 2022, my oncologist suggested that I begin a 1-year course of adjuvant immunotherapy. The protocol called for the administration of nivolumab (Opdivo, Bristol Myers Squibb) every 4 weeks for up to 1 year. After experiencing several toxicities, I made the difficult decision to stop treatment after just 6 of the planned 13 doses. What made the decision especially difficult was knowing just how much uncertainty existed regarding effectiveness and toxicity. We need to do whatever we can to reduce that uncertainty.

Disclosures

Dr Manski has no conflicts to disclose.

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