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Rightsizing the Dosing of Modern Oncology Drugs: Mind the Gap

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What could be more controversial than using lower than recommended doses of approved drugs, particularly for a life-threatening disease? But that is exactly what should be done for many anticancer drugs approved by global regulatory agencies. There are two potentially justifiable reasons for using lower doses: (1) reducing the risk and/or severity of adverse events and (2) reducing the cost of care. While not true of all marketed oncology drugs, it is expected that modern oncology drugs (e.g., kinase inhibitors, immunotherapy) would often be maximally effective at doses well below the maximally tolerated dose (MTD).[1] In contrast, the vast majority of dose-finding studies in oncology are simply phase 1 studies aimed at determining the MTD, rather than randomized dose-ranging trials to determine the optimal dose, as recommended by the International Committee on Harmonization E4 guideline.

Despite rapid evolution and advances in antineoplastic drug discovery, clinical trial paradigms have had only minor changes. Debate has focused on the optimal way to define the MTD, without considering whether or not the MTD is even relevant.[2] (To emphasize the point of lack of relevancy, the MTD of remdesivir, the first drug approved for coronavirus disease 2019, has never been ascertained). Furthermore, oncology drugs are often given in combination, which further complicates the challenges of dosing, if the optimal dose of the individual drugs has never been determined.

Historically, cytotoxic chemotherapy was usually administered parenterally, and thus, oncologists did not often have to consider the complexity of oral drug delivery, and certainly not the issues pertinent to many modern compounds, such as amphiphilic kinase inhibitors. While it was well known that food could increase drug absorption, the development of many oral oncology drugs has relied on fasting administration, perhaps due to a misperception that cancer patients might not be able to reliably take oral drugs with food.[3]

This mislabeling—at least from the perspective of a clinical pharmacologist—led to suggestions that some drugs could be administered at a fraction of the labeled dose, if administered off-label with food. Furthermore, a patient that did not strictly follow the labeled regimen (e.g., eating breakfast 30 minutes after the morning dose), could potentially suffer the consequences of an effective overdose due to greater absorption than in the clinical trials.[4,5] This has even led to the Food and Drug Administration (FDA) to require a black box warning in the U.S. nilotinib prescribing information for the risk of food causing sudden death, if consumed within 2 hours prior to or 1 hour after taking the drug.

The notion of using lower doses for the primary purpose of cost reduction has been dubbed "interventional pharmacoeconomics." [6] While regulatory agencies have occasionally required postmarketing studies of lower doses because of concerns regarding the safety of the initially approved dose, interventional pharmacoeconomic studies have rarely been initiated. As one example, Szmulewitz et al conducted a small prospective randomized study of low- dose abiraterone (25% of the standard dose administered off-label with food), which demonstrated that the lower dose—as expected based on the known effect of food to increase bioavailability of this agent—was essentially equivalent (and in fact noninferior) to the standard dose.[7] This reduced dose regimen, a 75% cost savings, was subsequently incorporated into the National Comprehensive Cancer Network guidelines as an acceptable alternative.

In India, abiraterone currently costs nearly INR 8,400 (US $110) per bottle of 120 tablets (250 mg), ostensibly a 1-month supply.[8] This is much cheaper than other oral

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anticancer agents, as abiraterone is manufactured and sold by multiple generic pharmaceutical companies. Yet, the annual cost of this generic drug is nearly 70% of the Indian per capita gross income.[8] Needless to say, new patent-protected agents are even less affordable, generally 5 to 10 times higher in monthly cost. The U.S. is no different, with some new agents having a list price of over US$30,000 (INR 2.3 million) per month, over US$360,000 (INR 27.4 million) per year (more than five times the U.S. per capita gross income).

While the notion of reducing the cost of abiraterone by 75% (i.e., stretching a 1-month supply to 4 months) is attractive, it is likely feasible to administer even lower doses per month, perhaps administering the drug as infrequently as weekly.[9] However, further studies are required before this strategy can be recommended.

While abiraterone is an excellent example of an overdosed drug, sotorasib may even be more egregious, approved in May 2021 by the FDA, but with a formal postmarketing requirement for Amgen to compare the labeled dose of 960 mg (administered as eight 120 mg tablets) to 25% of the labeled dose.[1] This requirement is justified due to a lack of a relationship of drug dose to both plasma concentrations and antitumor activity, which was evident at the lowest dose studied, 180 mg. Notably, an even lower dose (e.g., 120 mg) may be equally effective, as based on Amgen's preclinical data.

There are many other examples of both oral and parenteral drugs for which interventional pharmacoeconomic studies are indicated. There is no evidence of a dose–response relationship for ibrutinib, and the therapeutic index may be greatly enhanced by reducing the dose to 140 mg once daily (from 420 or 560 mg).[10] Multiple immune checkpoint inhibitors are also labeled at excessive doses, and reduction of dose and/or frequency will certainly reduce costs, and potentially toxicities as well.[11]

We have made great advances in the treatment of cancer, and now the pharmaceutical industry is holding the world economically hostage—at least for payers and patients seeking access to their modern drugs. While companies should be appropriately incentivized to discover, develop, and commercialize drugs, physicians and patients should expect, if not require, that drug doses be optimized, particularly for those drugs that can cause significant toxicities interfering with patient quality of life. While the FDA has taken the lead on requiring dose optimization for new drugs, governments also need to enable and support (if not require) dose optimization studies for already marketed drugs, particularly if there is evidence that the marketed dose is excessive.

This is an important global gap in oncology clinical research and best practices. Instead, patients in wealthier countries receive unnecessarily high—and often toxic—doses of drugs, whereas patients in low- and middle-income countries often do not have access to modern drugs at all.

Conflict of Interest
None declared.

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