

Modifying drug dosages in oncology: immense need for innovative oncology treatments

Editorial

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Accelerated clinical development of anticancer medications is essential to guarantee that patients receive the safest and most efficient care possible. Simultaneously, the development procedure ought to be planned to guarantee that the ideal dosage and timing are applied. Consequently, to guide cancer medication development and dosage optimization, pharmacologic techniques including pharmacogenomics (PG), pharmacokinetics (PK), and pharmacodynamics (PD) must be integrated.

The goal of PG is to understand how genetic variations affect the toxicity and effectiveness of drugs. This term was used for the first time by the geneticist F. Vogel in the late 1950s. Years later, the genetic variations of the cytochrome P450 2D6 (CYP2D6) gene were identified as the cause of the altered metabolism^[1]. Germline variants, epigenetic variants, modifications in gene expression profiles, and structural chromosomal changes are some of the most frequently studied genomic variations. These genetic differences can be somatically acquired or genetically inherited.^[2]

Throughout the drug development process, important decisions can be informed by the aforementioned pharmacologic disciplines. PK and PD play a critical role in defining and choosing the candidate molecules to be tested in everyday clinical practice, throughout the discovery and preclinical development phases. Pharmacogenomics (PGx) may also be useful in identifying particular patient populations and drug targets. During the initial stages of clinical development, phase 2 and 3 study dose selection could be done using

PGx-guided, PK-guided (therapeutic drug monitoring [TDM]), and PD-guided methods. PGx and PK/PD may offer strong evidence for dose optimization, exposure-response (E-R) relationships, and support for regulatory submissions and approvals in later stages of clinical development. In conclusion, post-marketing PGx and PD in phase 4 research may be very useful in defining possible side effects^[3].

In most therapeutic areas, drugs are assessed through pivotal, randomized, dose-ranging trials. Robust data, have been provided by several studies, in order to comprehend and characterize the effect of drug dose on both efficacy and toxicity. However, in the field of oncology, there exists a pressing necessity for prompt access to innovative, efficacious, and transformative therapies. Therefore, it may not be feasible to follow a sequential phase 1-3 trial paradigm for optimal dose selection before approval^[4]. Dose-ranging research is, therefore, mostly restricted to phase 1 first-in-human (FIH) clinical trials. Moreover, the primary goal of the oncology FIH design is to determine the maximum tolerated dose (MTD) by searching for dose-limiting toxicities (DLTs) during the first cycle of treatment or by determining the highest tested dose (HTD) in the event that no DLTs are found^[5].

Monoclonal antibodies (mAbs) target and kill cancer cells through a variety of mechanisms, such as complex antibody-dependent cellular cytotoxicity (ADCC) mechanisms, immune system stimulation through binding to antigen(s) on the cell surface, immune system activation through immune checkpoint protein

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blocking, and inhibition of growth factors on cancer cells^[6]. While some mAbs have unique (E-R) profiles, there has not been much research done on TDM or this has not been used in clinical settings. The difficulty of quantifying mAbs in plasma due to bioanalytical issues limits the use of TDM for mAbs. The complicated PK of mAbs, their broad therapeutic windows, and the lack of usual characterization of E-R relationships linked to clinical efficacy may restrict the application of TDM for customized dosing. In contrast to tyrosine kinase inhibitors (TKIs) and conventional cytotoxic chemotherapy, TDM-based dosing has not been extensively documented^[7].

In conclusion, choosing the right dose for new anticancer drugs is a constant struggle. A successful development plan depends on the design of early clinical studies based on the pharmacologic characteristics of the drugs, but this is not always possible because it necessitates quick approval after a series of phase

1–3 trials. Experience has shown that, in most cases, a customized approach to dosage based on each patient's unique characteristics and each drug could enhance treatment efficacy and safety. Currently, the standard 3 + 3 design is used in clinical trials to evaluate DLTs. This method works well and provides useful information for older cytotoxic drugs, but there are issues with more recent modalities like TKIs, biologics, and antibody-drug conjugates (ADCs)^[3].

In the present issue, there is a very interesting article about the changing of dosing paradigm in oncology. More specifically, the article deals with re-evaluating the well-founded theory that the dosage of a drug determines its effectiveness, because many molecules appear to be effective at even the lowest doses possible, while posing the least amount of toxicity^[8]. There are also other interesting articles about many tumor types covering a wide area in the field of medical oncology.

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