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PERSPECTIVE

US Food and Drug Administration embraces using innovation to identify optimized dosages for patients with cancer

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Given evidence that currently used dosing regimens are not tolerable for many patients with cancer, the public has expressed an urgent need to optimize dosages for oncology drugs. Many dose-finding trials (e.g., 3 + 3) are designed to identify the maximum tolerated dose (MTD) based on dose-limiting toxicities (DLTs) documented within the first cycle (i.e., 28 days); this paradigm was initially implemented for cytotoxic chemotherapy based on their typically steep dose–response curve and the assumption that higher doses are more efficacious for this fatal disease. This paradigm unfortunately often leads to dosages that are inadequately characterized during development and that result in substantial toxicity. With the emergence of targeted therapies and immunotherapies and improvement in the long-term prognosis for many cancers, we believe that oncology drug development needs to embrace new approaches that consider all available clinical and nonclinical data (not just short-term safety data) in real time. Translational strategies that iteratively evaluate emerging data should be considered to increase the likelihood of identifying dosages that optimize the long-term benefits and maintain the quality of life of all patients with cancer. To that end, we support using innovative approaches that can facilitate the development and application of alternative dose-finding methods either alone or in conjunction with the well-established strategies to the ultimate benefit of patients.

OUR HISTORY

The US Food and Drug Administration (FDA) Office of Clinical Pharmacology (OCP) has long recognized the inherent tension between ensuring expeditious access to promising new drugs and conducting thorough investigations to elucidate the underlying drivers of response variability. Patient factors (i.e., age, race and ethnicity, and organ impairment), disease factors (i.e., genomic and molecular variation in the purported drug target), and

their interactions can result in the need for individualized dosages at the patient- or subpopulation-level and may necessitate different trial designs and analytical approaches from those of the past. In response, we have actively engaged with patients, caregivers, advocacy groups, drug developers, and academia to reconcile this tension and re-imagine dosage optimization strategies. The recent launch of the FDA Oncology Center of Excellence Project Optimus[1] has allowed our ongoing efforts to gain substantial momentum. Interdisciplinary scientists involved with this project have raised awareness by providing regulatory advice on innovative, non-traditional approaches to dose-finding, developing instruments to facilitate efficient regulatory assessment of emergent information relevant to investigational new drug dosage optimization, participating in public meetings, and supporting education and research. As an example, preliminary findings from our research support the need for dosage optimization for oncology drugs in the premarket setting. Our findings show that many new drugs required postmarketing trials to explore alternative dosages to that of the originally approved recommended dosage; these investigations generally involved a large, resource-intensive, multi-year trial (median 6 years) with substantial patient enrollment,[2] suggesting some patients may be exposed to suboptimal dosages. The FDA recently published a draft guidance titled, "Optimizing the Dosage of Human Prescription Drugs and Biological Products for the Treatment of Oncologic Diseases"[3] to facilitate dosage optimization for oncology drugs and we are currently evaluating public input before finalizing our policy. We believe that these multistakeholder collaborations will continue to be instrumental in reshaping our approach to dosage optimization for all patients with cancer (including older adults and pediatric patients), such as the development and application of novel trial designs and analytical methods.

INNOVATIVE TRIAL DESIGN AND ANALYSES

Alternative trial designs and analytical methods with an iterative process that leverages nonclinical data and clinical observations beyond short-term safety data are needed to identify optimized dosages for newer oncology drugs, given targeted therapies and immunotherapies often do not demonstrate traditional DLTs and meaningful clinical activity may be observed at dosages lower than the MTD.[4] Controlled backfill,[5] strategically planned expansion cohorts, and randomized parallel dosage comparisons can yield additional clinical data to increase confidence that dosages carried forward into registration trials have been optimized. With evolutions in methodology and growing regulatory experience with model-informed drug development (MIDD), the FDA is increasingly interested in implementing model-informed clinical trial designs (e.g., algorithm-based Bayesian designs). Although these approaches are relatively new compared with traditional toxicity-driven dose-finding trials, they may allow for more informative dosage selection in situations where nonclinical data, same-in-class drug information or emerging clinical data can be maximally leveraged. The FDA has, in fact, deemed several model-informed approaches (e.g., MCP-Mod, BOIN design, and empirically based Bayesian maximum effect [E_{max}] models) "fit-for-purpose"[6] in certain contexts of use and welcomes additional research and discussion on the trade-offs between toxicity-driven approaches and novel model-based holistic approaches.

We also understand the practical challenges in identifying an optimized dosage before drug approval. To that end, we are interested in the adoption of seamless, adaptive designs[7] to address key questions around optimized dosage, safety, and efficacy determination. Possible approaches currently being evaluated include comparing multiple dosages prior to or as part of a registration trial after an expedited proof-of-concept. We also encourage a clearly delineated plan for robustly establishing dose- and exposure-response relationships (e.g., by prespecifying the approach to evaluating the association between relative dose intensity and clinical outcomes). Post hoc dosage refinement (which has been our historical approach out of necessity) has well-documented limitations given only one dosage is typically evaluated in registration trials.[2,8] This limits the robustness with which we can infer an optimized dosage has been derived, further supporting the need for evaluating dose- and exposure-response relationships to inform the dosages to be evaluated in efficacy trials.

LOOKING AHEAD

Whereas our immediate focus has largely been on alternative trial designs and analyses; we seek other opportunities to better inform dosage optimization. Advancement in biomarker science, for example, presents an exciting opportunity to integrate pharmacokinetics (PKs), pharmacodynamics (PDs), safety, tolerability, and tumor response data to gain better understanding of the relationship among various drug exposure metrics, safety, and efficacy. Development of soluble markers of tumor pathogenesis and disease-modifying pharmacological activity could be greatly enabling toward that end. In addition, coupling PK/PD analyses with novel methods to identify predictors of patient response variability (e.g., via machine learning approaches) could serve

as a powerful approach to de-risk both dosage selection and clinical development. Furthermore, the movement away from small molecule drug development toward novel therapeutic platforms (e.g., antibody-drug conjugates, and bispecific and trispecific antibodies) tracks with evolving understanding of biological complexity in cancer. Mechanistically informed in silico approaches that leverage that understanding (e.g., digital twinning to construct virtual populations) may be helpful for predictive biomarker identification and dose–response characterization. Indeed, recent data suggest mechanistic modeling and simulation (quantitative systems pharmacology in particular) is being used to inform a wide range of clinical trial designs, clinical development, and regulatory decisions for immunotherapies, including for dosage optimization and biomarker selection.[9] As an example, a quantitative systems pharmacology modeling platform that was built to describe complex interplay among immune cells, cancer cells, immunotherapy, and other relevant factors is being used to evaluate various immunotherapy combinations to predict patient outcomes in virtual trials.[10] Finally, once a new drug is approved, it is often then used in populations that are much more heterogeneous than the population studied in the clinical trials that supported its approval. Although we believe that translational strategies discussed here could be applied to all patients with cancer, including historically under-represented populations, such as older adults, pediatric patients, and rare cancers, we recognize that the dosage identified at the time of drug approval, in fact, may not be optimized for "real-world" patients. This question is fostering the growing interest in how to leverage real-world data to further refine previously approved dosages. Although the use of real-world data is not without its own methodological constraints, we do support the concept of dosage optimization as one that occurs across the drug lifecycle and welcome discussion on how real-world data can be appropriately leveraged to optimize dosages based on patient-specific factors.

COLLABORATION AND ENGAGEMENT

The successful implementation of innovative trial designs, analytical methods, and emerging science requires ongoing, open dialogue with multiple stakeholders (including additional regulatory agencies). The FDA scientists work collaboratively to provide regulatory advice on specific regulatory submissions, drug development programs, drug development tools, and novel approaches in a variety of forums. For example, our office leads the Center for Drug Evaluation and Research (CDER) MIDD Paired Meeting Program,[11] which continues to advance and integrate development and application of exposure-based, biological, and statistical models in drug development and regulatory review. This program has resulted in a positive impact on drug development, including reduction in clinical development time, reduction in the number of patients unnecessarily enrolled into clinical trials, more expeditious attrition of investigational new drugs unlikely to make it to the clinic, and millions of dollars saved.[12] The program has been used to enable scientific and regulatory alignment on various issues, including dosage optimization, and the majority of meetings have been conducted in the oncology therapeutic area. Additional opportunities to engage with the FDA include regulatory milestone meetings, clinical pharmacology-led type C meetings, and other newer meeting types (i.e., type D, a meeting focused on no more than 2 topics requiring no more than 3 disciplines) for specific drug products, as well as meetings to discuss novel methodologies and technologies (i.e., Critical Path Innovation meetings[13]). We welcome creativity and innovation in dosage optimization and encourage meeting with us using various available avenues, and developing other forums if needed, to continue the dialogue on dosage optimization for patients with cancer.

The programs, initiatives, and tools described here showcase means and methods to identify an optimized dosage for patients with cancer. No "one-size-fits-all" approach will be appropriate for every development program and disease context. That said, as treatment for cancers becomes more chronic, with some patients taking oncology drugs for years, it is imperative that optimized dosages be identified for all patients before drug approval, with an understanding that some adjustments may be necessary along the way as our understanding of drug safety and drug response variability expands. We are working with the stakeholder community to pivot to a more proactive and intentional paradigm with regard to dosage optimization.

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CONFLICT OF INTEREST STATEMENT

The authors declared no competing interests for this work.

DISCLOSURE

The views expressed in this perspective are the authors' views alone. They do not reflect the official views or guidance from the US Food and Drug Administration, nor should they be construed as such.

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