A Regulatory Perspective on Dose Optimization for Oncology Products

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May 13, 2023

Introduction

According to the World Health Organization (WHO, 2022), cancer is the primary cause of death worldwide. This serious disease is highly complex, and treatment varies depending on the disease stage, the cancer's location, and molecular aberration. Therefore, the FDA has prioritized the development of oncology products to improve the lives of cancer patients. Sponsors can use accelerated approval, fast-track designation, and breakthrough designation pathways (FDA, 2014) to expedite the drug development process for oncology drugs. Speed to market has always been a crucial factor in the development of oncology drugs.

As Friends of Cancer Research points out, it is standard practice for non-oncology drugs to undergo randomized dose-ranging trials (i.e., Phase II) to select the optimal dose. Historically, dose-finding trials for oncology products were limited to phase 1, where the goal was to determine the maximum tolerated dose (MTD) (FDA, 2023). Reliance on the MTD assumes that more is better.

The MTD paradigm was useful for cytotoxic chemotherapy drugs, which have “steep dose-response curves” and lack the specificity for newer-generation medicines (FDA, 2023). These newer generation drugs, such as kinase inhibitors and monoclonal antibodies, have higher specificity for their target and different exposure-response curves than cytotoxic drugs. Therefore, relying on the maximum tolerated dose for such agents may not be appropriate.

The FDA has raised concerns regarding the MTD approach and called for Sponsors to determine the optimum dose based on the drug’s efficacy, safety profile, and exposure-response relationship. According to the FDA, the use of the MTD paradigm for molecularly target agents can result in a dosage that is “poorly tolerated, adversely impacts the functioning and quality of

life, and affects the patient's ability to remain on the drug and thereby derive maximal clinical benefit" (2023).

Food and Drug Administration Perspective

The FDA is attempting the shift the paradigm from using MTD as the dose for oncology drugs. Instead, they advocate for evaluating a range of doses to understand the exposure-response relationship. This approach is similar to the drug development process used for other therapeutic areas. Consequently, the Agency has released the following guidance entitled "Optimizing the Dosage of Human Prescription Drugs and Biological Products for Treatment of Oncologic Diseases" in 2023. This guidance summarizes the challenges of relying on the MTD paradigm for dose selection and provides recommendations on optimizing the dose.

The FDA has clearly stated in their guidance that the dose selected at each stage of development, i.e., (phase 1, phase 2, phase 3, and marketing) should be supported by the relevant clinical and nonclinical data (FDA, 2023). Sponsors should discuss their plans to optimize the dose of their product through FDA meetings. The use of expedited pathways does not justify the lack of dose optimization. The FDA will issue a clinical hold if they determine that the selected dose poses an unreasonable safety risk to patients (FDA, 2023). For marketing applications, lack of an optimized dose can result in failure to obtain marketing approval or require additional clinical trials to demonstrate safety and efficacy in that population.

Perceived Challenges

There are a few perceived challenges with the widespread adoption of dose-finding trials for oncology products in the early phase setting. One primary concern is that conducting such trials will be time-consuming and potentially delay patients' access to these medicines(FOCR,

2021). However, Friends of Cancer Research (FOCR) argues this perception is misguided and highlights the risks of not optimizing the dose before the pivotal trial.

According to FOCR, using an unoptimized dose in the pivotal trial will make it challenging to identify the true benefit of the drug. Taking the extra time to improve the dose can improve tolerability, impacting patients' ability to remain on treatment and derive benefit (FOCR, 2021). Unfortunately, many oncology drugs have high rates of dose reductions and discontinuations. The FDA has noted this and has issued post-marketing commitments to study alternative dose schedules or doses. As Kim et al. (2016) pointed out, this has been a point of concern for a class of drugs known as kinase inhibitors, where 8 out of the 31 approved drugs have post-marketing requirements or commitments related to dose optimization. Therefore, it is crucial for Sponsors to determine the appropriate dose for patients before the dose is approved. Performing dose optimization in the early phase setting will lay the groundwork for future drug development. In addition, Proper dose optimization can avoid clinical holds and the need for costly post-marketing requirements.

A second barrier to adopting randomized dose-finding studies in early-phase clinical trials is the perception that lower drug doses are less effective than higher doses (FOCR, 2021). This perception may exist among clinicians, investigators, and companies involved in drug development due to the longstanding reliance on MTD as the selected dose for pivotal trials. Friends of Cancer Research advocates that this challenge can be overcome through transparent communication with stakeholders. Evaluation of lower doses does not always correlate to less efficacy. Providing transparency to investigators concerning how the dose(s) were selected based on the unknown and known aspects of the drug will go a long way in breaking this assumption down. Similarly, patients should be informed of the utility of studying lower doses through the

informed consent process (FOCR, 2021). Ultimately, transparent communication is essential in shifting the paradigm from MTD to randomized dose-finding studies. The following section will discuss strategies Sponsors can use to optimize the dose.

Methods to Optimize the Dose

Phase 1 clinical trials commonly use the 3 + 3 design to determine the maximum tolerated dose (MTD) during a specified period called the dose-limited toxicity (DLT) period (Kim et al., 2016). This period typically lasts for 28 days, during which the patient's condition is closely monitored for any signs of toxicity. However, some researchers, like Kim et al., have criticized this design for not fully capturing the safety and tolerability of kinase inhibitors, which can have delayed toxicity that is not reflected in the DLT period (2016). Therefore, it is important to consider toxicities beyond this period to get a more comprehensive understanding of the drug's tolerability.

Patient-reported outcomes (PROs) can be a useful tool for sponsors to assess the tolerability of a drug. PROs are assessments that allow patients to report on the severity and magnitude of any adverse events they experience during a clinical trial. It has been noted by Friends of Cancer Research that clinicians may underestimate patient symptoms and overestimate functional status (2021), making PROs a valuable resource. However, it is important to recognize that implementing PROs must be done with care as it can introduce bias and place additional burdens on patients. Sponsors should carefully consider which PRO data to collect, and how to collect it. By combining PRO data and investigator-reported adverse events, a better understanding of drug safety and tolerability can be gained.

When it comes to selecting the appropriate dose for a drug, Ji et al. (2018) recommend taking into account a variety of factors, including pharmacokinetic, pharmacodynamic, non-

clinical, and clinical data. This requires a comprehensive evaluation of all known and unknown information regarding the drug. Ji also suggests considering different phase 1 designs, such as the Bayesian model-based design. One such design, the Bayesian Optimal Interval (BOIN) design, utilizes data from the entire clinical study to determine when it is appropriate to move to the next dosage level. According to Zhou et al. (2020), the BOIN design is more precise in determining the maximum tolerated dosage (MTD) and is ultimately safer for patients.

The FDA recommends evaluating multiple doses in a clinical trial to provide confidence in the dose used for marketing applications (FDA, 2023). To mitigate bias, a randomized phase II trial is the gold standard. An alternative approach includes studying multiple dose levels in the pivotal phase study. However, it's important to note that phase III studies are the largest and most expensive, so evaluating multiple dose levels earlier in development can save time and unnecessary expenses. Sponsors must understand their drug at different dose levels before submitting the marketing application. In the next section, we will discuss a case study highlighting the impact of submitting a marketing application without an optimized dose.

Poziotinib Case Study

Spectrum Pharmaceuticals submitted a new drug application (NDA) in 2021 for Poziotinib under the accelerated approval pathway. Accelerated approval (AA) is reserved for drugs that provide an advantage over available therapies and have demonstrated an effect on an endpoint that is reasonably likely to predict clinical benefit (FDA, 2014). In addition, drugs that are granted AA are required to verify the clinical use in a subsequent trial, known as a confirmatory trial. The proposed indication in the NDA application was for the “treatment of patients with previously treated locally advanced or metastatic non-small cell lung cancer

(NSCLC) harboring human epidermal growth factor receptor 2 (HER2) exon 20 insertion mutations" (FDA, 2022a).

Poziotinib was studied as a single agent in a global, non-randomized, dose-finding study in the proposed patient population for NSLC, with patients receiving doses ranging from 10 mg to 16 mg. The overall response rate was 28% for patients treated with a median duration of response of approximately five months. In contrast, the available therapy (i.e., chemotherapy) has overall response rates of up to 23% with a median duration of response of up to 16 months when combined with an anti-PD(L)1 drug. According to the FDA, if Poziotinib were granted AA based on these results, it would be the least effective molecularly targeted therapy in the lung cancer setting ever (FDA, 2022a).

Moreover, the FDA states that the proposed dose for poziotib is poorly tolerated, as indicated by the high rate of adverse events at 88% of patients in the Zenith20 study undergoing treatment interruption or dose reductions (2022a). The high rate of adverse events and dose reductions reflects inadequate dose optimization on behalf of the Sponsor. The FDA performed an exploratory analysis to evaluate the impact of exposure on the safety and efficacy of Poziotinib. The results of their analysis suggested that an alternative dose may improve safety while providing similar efficacy (FDA, 2022a).

The FDA convened an Oncologic Drugs Advisory Committee (ODAC) to discuss the benefit-risk profile of Poziotinib in the proposed patient population of NSLC patients with external stakeholders that include clinicians and patient advocacy groups. At the ODAC, committee members were asked to vote on whether the benefits of Poziotinib outweighed the risks for the treatment of HER2-positive NSLC patients (FDA, 2022 b). The final vote was 4 to 9, with 4 in favor and nine voting against. Committee members raised concerns regarding the

lack of dose optimization, tolerability concerns, and lower overall response rate. Consequently, Spectrum Pharmaceuticals did not receive accelerated approval for their drug and must continue dose optimization efforts before re-submitting their NDA.

Conclusion

As we work towards developing new drugs for oncology, it is important to prioritize dose optimization in the clinical development process. Neglecting this crucial component could lead to adverse events for patients and ultimately hinder drug development progress. With the shift towards molecularly targeted therapies, it is even more imperative that we bring our drug development paradigm up to speed. While dose optimization may require more time and resources, the benefits for patients, the industry, and our healthcare system are worth the investment. It is time to be intentional in selecting the right dose for our products to ensure the best possible outcomes for cancer patients.

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