ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

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New Strategies for Dose Optimization in Oncology: Insights From Targeted Small-Molecule Therapies for Metastatic or Advanced Non–Small Cell Lung Cancer

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H&O What types of tyrosine kinase inhibitors are used to treat metastatic or advanced non–small cell lung cancer (NSCLC)?

GS There are 2 broad categories of metastatic or advanced non–small cell lung cancer (NSCLC) that guide selection of treatment: cases that are driven by clear-cut, oncogenic mutations and those that are not. Treatment of oncogene-driven cancers is based on receptor tyrosine kinases and intracellular tyrosine kinases. Receptor tyrosine kinase mutations, fusions, or copy number variants in NSCLC can include those in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), c-ros oncogene 1 (*ROS1*), neurotrophic tyrosine receptor kinase (*NTRK*), the *RET* proto-oncogene, and mesenchymal-epithelial transition (*MET*), among others. Commonly used drugs include osimertinib (Tagrisso, AstraZeneca), afatinib (Gilotrif, Boehringer Ingelheim), erlotinib, and gefitinib (Iressa, AstraZeneca) in *EGFR*-mutated NSCLC; alectinib (Alecensa, Genentech), brigatinib (Alunbrig, Takeda), and lorlatinib (Lorbrena, Pfizer) in *ALK* fusion–positive NSCLC; crizotinib (Xalkori, Pfizer), entrectinib (Rozlytrek, Genentech), and ceritinib (Zykadia, Novartis) in *ROS1*-mutated NSCLC; larotrectinib (Vitrakvi, Bayer) and entrectinib in *NTRK*-mutated NSCLC; agents such as selpercatinib (Retevmo, Lilly) and pralsetinib (Gavreto, Blueprint/Genentech) in *RET* fusion–positive NSCLC; and capmatinib (Tabrecta, Novartis) and tepotinib (Tepmetko, EMD Serono) in NSCLC characterized by *MET* exon 14 skipping alterations. Treatment of patients with refractory NSCLC can also include monoclonal antibodies that target receptor tyrosine kinases. Occasionally, patients with NSCLC have a mutation in human epidermal growth factor receptor 2 (HER2). In this subgroup, trastuzumab and associated therapies have been effective.

Patients can also have mutations in intracellular serine/threonine kinases and receive inhibitors that target them, such as the BRAF inhibitors. These treatments include vemurafenib (Zelboraf, Genentech) or dabrafenib (Tafinlar, Novartis) as a single agent or in combination with cobimetinib (Cotellic, Genentech) or trametinib (Mekinist, Novartis), respectively.

H&O How were the original doses of these drugs established?

GS Developing these drugs' dosing regimens reflects the way chemotherapy agents were developed throughout the mid-20th century, in which clinical trials tethered the selected dose to the probability of side effects. The original dosages for newer targeted therapies were identified through phase 1 clinical trials that slowly escalated the dose until some toxicity threshold was reached. With this approach, dose selection is immediately tied to toxicity.

There may be a better strategy.

None of the treatments that I mentioned above went through randomized dose-ranging studies, in which patients are randomly assigned to receive one of multiple different doses of the same drug. Prospective data comparing different dose levels are lacking. Therefore, the pivotal phase 3 studies that compared overall survival with a new drug vs the standard of care utilized a dose that was not compared with other doses and, consequently, may not optimally balance efficacy and toxicity. Maybe that will change in the future. Under the dose-optimization paradigm from the Oncology Center of Excellence at the US Food and Drug Administration (FDA), mainly under the leadership of Project Optimus, the old pattern of moving a drug forward into a pivotal trial without dose optimization will likely change. This development will be fortunate for clinicians and patients who are concerned about safety.

For many of the newer, targeted therapies, an increase in the amount of drug that reaches a cancer cell does not necessarily equate to improvements in efficacy.

H&O What are the indications that a dose adjustment would be beneficial?

GS For an individual patient, a dosage adjustment might be warranted in the event of an undue clinical toxicity, particularly if it threatens the ability of a patient to safely remain on that therapy. This decision is especially difficult when the patient is clearly deriving benefit from the therapy. Unfortunately for a lot of patients, toxicities of treatment accumulate over time. A physician might need to lower a dose in response to these toxicities.

At the broader level, it is necessary to consider whether the selected starting dose of a drug is optimal for an entire population. This decision is more difficult. There are a few metrics included in pivotal clinical trials, and sometimes even in earlier-phase studies, that might indicate whether a selected dose level could be suboptimal at a population level. For example, data from a large pivotal trial might show relatively high rates of treatment discontinuation for the experimental targeted therapy, because in many cases patients discontinue therapy owing to side effects. One could reasonably argue that the discontinuation rate for an appropriately-dosed targeted therapy should never be lower than the discontinuation rate for a drug that is not targeted. If the discontinuation rates are the same, this could very well reflect off-target toxicity. A trial might also show a high rate of patients in the targeted therapy arm who require a dose reduction. There might be elevated rates of grade 3 or higher toxicities. Interpretation of these studies requires a totality-of-data approach. The presence of one or more of these warning signs combined with pharmacokinetic data from earlier-phase studies can raise questions regarding the appropriateness of a given drug's dosage. Physicians constantly ask themselves whether patients are receiving optimal treatment; they should also be questioning whether the amount of the treatment they are providing is optimal.

For many of us, it is disappointing to see new drugs—which are borne out of highly elegant preclinical science—come to market at dosages that produce avoidable toxicities as a function of having skipped a randomized dose-ranging study. I also worry that the existing paradigm allows physicians to accept the idea that all cancer treatments must be toxic in order to generate benefit, and leads to patients internalizing this idea, too.

H&O What were your findings about the dosing of lorlatinib?

GS It is interesting to note that looking at the data from a different perspective can sometimes tell a different story. For example, Dr Mark Ratain and I published a letter to the editor in which we viewed the pharmacokinetic data for lorlatinib through the lens of clinical oncology. Frequently, increasing the dose of a drug increases the amount of the drug in the circulation that can affect the cancer (the "exposure"). For drugs such as chemotherapy, increases in exposure were thought to correspond with increases in efficacy. This correlation led to the foundational assumption that permeates much of cancer drug development: that more drug is automatically better. With a lot of drugs, though, there are no free lunches: increases in exposure come with a higher risk of side effects.

For many of the newer, targeted therapies, an increase in the amount of drug that reaches a cancer cell does not necessarily equate to improvements in efficacy. Increases in drug exposure might do nothing except increase side effects. Our letter about lorlatinib highlighted the need to minimize the toxicity associated with treatment of

metastatic NSCLC, which is generally considered to be incurable. An interesting finding about lorlatinib is that increasing lorlatinib's exposure did not increase its efficacy. Increasing lorlatinib's peak exposure did increase its toxicity in terms of grade 3 or greater cholesterol issues that could predispose to serious clinical issues and required treatment, and cumulative exposure increased the probability of having grade 3 or greater adverse events. This finding raises the question of why a drug would be administered at a dose known to increase adverse events unless there is a compensating clinical benefit. Physicians automatically think about risks and benefits when making clinical decisions, and they need to discuss those risks and benefits with patients. The same considerations should be at the forefront of drug development.

The lorlatinib example shows just how difficult it is to identify the single best dose from early-phase trials, which are too small to indicate whether one dose level is clearly more efficacious or toxic than another. Taking a totality of data approach that includes pharmacokinetic data (and ideally, a randomized dose-ranging study in the premarket setting) increases the probability of identifying the optimal dose.

H&O What are the potential consequences of treatment with a suboptimal dose?

GS As a health services researcher, I break this question down into individual-level consequences and societal-level consequences. For individual patients, the potential consequences can include treatment-related side effects so severe that the drug needs to be stopped altogether, the treatment needs to be paused, or the treatment does not need to be stopped but quality of life is diminished. Any one of these outcomes might represent a missed opportunity to improve both the quality and quantity of a patient's life. It is possible that the drug could have been effective for the patient if only it had been administered at an optimal dose.

At a health services level, adverse events can require hospitalization. Adverse events can necessitate cascades of further diagnostic testing or themselves require treatment, like with lorlatinib. The possibility of these harmful downstream events is a strong incentive to optimize dosing before the drug enters the clinic.

H&O How does quality of life fit into dose selection in oncology?

GS The quality-of-life metrics that are evaluated in pivotal clinical trials, and even in some phase 2 studies, are not typically included in phase 1 studies. Early-phase clinical trials tend to focus on the presence or absence of dose-limiting toxicities. In many cases, early-phase clinical trials or even updated Bayesian-style clinical trials aim to identify a dose level that will generate side effects at some prespecified rate. Consequently, we are hard wiring into drug development the expectation that a cancer therapy will make patients sick at some prespecified rate. However, many oncologists, regulators, and patients think we can do better, and we seem to be moving in that direction.

H&O Are there newer ways to establish the dose of a drug and/or dose modification strategies?

GS It is important to recast phase 1 as a learning phase of drug development. Ideally, the goal of early-phase studies should be to identify the range of dose levels that can then be tested in randomized dose-ranging trials. These early randomized studies can then identify preliminary signs of efficacy and can help inform which dose to take forward in a pivotal clinical trial. Some emerging statistical methods are aimed at identifying—based on phase 1 data—a plausible range of dose levels that can be assessed in a randomized manner.

Again, the goal is to take a totality of evidence approach, so readouts that measure the extent of target engagement and other pharmacodynamic indicators, as well as early markers of antitumor effects (such as circulating tumor DNA) can be used in tandem with some of the newer trial designs to help expedite the timeline of drug development, while permitting a greater focus on dose optimization than is possible now.

H&O Can the insights gained from dose optimization of these drugs be applied to other settings?

GS I think they can. In the premarket setting, before a drug receives regulatory approval from the FDA, oncology appears to have some catching up to do with other branches of medicine. In other fields, randomized assessments of different doses are relatively common. Oncologists are also focusing on the doses of drugs that are already approved. Innovations from oncology, in terms of both clinical trial design and use of surrogate markers, may end up being instructive for other fields.

As a health services researcher, I tend to view these issues through a lens of scarcity. A perhaps idiosyncratic idea is that the optimal dose for a given drug may vary with on-the-ground conditions. It is necessary to think about the goals of the optimization process for each specific situation. Take a scarce vaccine, for example. In the interests of maximizing a population's level of protection, it might be prudent to administer a scarce vaccine at a dose that is lower than the dose level that produces the

highest level of efficacy for the individual. Increasing the pool of patients who can benefit from a scarce resource might improve outcomes for the overall population. In order to make those decision with confidence, however, you have to have an understanding of the relationship between dose and efficacy.

H&O Are there any other areas of research concerning dose optimization?

GS The concept of optimizing the dose is important for different lines of therapy. In many cases, dose-optimization studies or early-phase clinical trials evaluate later lines of therapy. These patients have already received many drugs and might not be able to tolerate another one. How we think about the propensity for developing side effects, and what the clinical consequences of those side effects are with respect to the ability continue on treatment, merit consideration. Does that make the maximum dose necessarily the best dose in earlier lines of treatment? Probably not. For some of these diseases, patients will remain on therapy for many years. We also need to think about dose optimization in combination therapies. If we are going to say that a combination of therapies can generate efficacy that is greater than the sum of its parts, then we should also acknowledge that toxicities could be greater than the sum of the parts. Dose optimization still makes sense there. Altogether, the area of dose optimization is an exciting, evolving science.

Disclosure

Dr Strohbehn is an employee of the Department of Veterans Affairs; this interview represents his personal views and not the position of the US Federal Government. Dr Strohbehn is a co-inventor of filed provisional patents in the postmarketing dose-optimization space, and is an uncompensated director of the Optimal Cancer Care Alliance, an Ann Arbor, Michigan–based 501(c)3 organization.

Suggested Readings

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