ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Redefining Dose-Limiting Toxicity

Sophie Postel-Vinay, MD, PhD
Drug Development Department
Institut Gustave Roussy
Villejuif, France

H&O How are dose-limiting toxicities currently determined?

SPV Dose-limiting toxicities (DLTs) traditionally are defined by the occurrence of severe toxicities during the first cycle of systemic cancer therapy. Such toxicities are assessed according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) classification, and usually encompass all grade 3 or higher toxicities with the exception of grade 3 nonfebrile neutropenia and alopecia. This broad definition dates back to the development of conventional cytotoxic chemotherapeutic agents, and is not applicable to the toxicity profile of modern molecularly targeted therapies (MTTs), which now constitute the vast majority of drugs evaluated in phase 1 trials. Despite this shift in drug development, the old definition of DLT is still used for most clinical trials. However, a few clinical trials are beginning to update their definition of DLT, and now tend to add variations to that common DLT definition backbone. The most frequent changes include the addition of some a priori untreatable or irreversible grade 2 toxicities (eg, neurotoxicities, ocular toxicities, or cardiac toxicities), prolonged grade 2 toxicities (ie, grade 2 toxicities lasting longer than a certain period), or the prolongation of the DLT period. However, these changes are still rare and most phase 1 clinical trials still use the traditional DLT definition.

H&O Why is the current definition of DLT ineffective?

SPV The current definition is ineffective because MTTs profoundly differ from conventional cytotoxic chemotherapy in several aspects. First, conventional cytotoxic chemotherapies are most often administered for a delimited period, and then halted for safety reasons, even if some degree of tumor response is still being observed. In contrast, MTTs are administered until resistance occurs or the patient experiences intolerable toxicity. Some moderate toxicities that affect quality of life (eg, grade 2 diarrhea or dry mouth) can become intolerable when they last longer than a certain period, and therefore deserve more attention. Similarly, the current DLT definition does not assess delayed or cumulative toxicities, which can lead to dose reductions or therapeutic pauses.

Second, the dose-efficacy relationship of cytotoxic agents typically is monotonic; that is, the slope of the curve increases or decreases over the entire dose range. This is not always true for MTTs and is not applicable to immunostimulatory agents, for which the maximum tolerated dose (MTD) sometimes is not even reached. Therefore, these agents usually display a larger therapeutic window, and the best recommended phase 2 dose might not be the MTD or the highest evaluated dose. Lower doses that are between the MTD and the optimal biological dose (ie, the dose at which pharmacokinetic and pharmacodynamics parameters are satisfactory) may be used with similar efficacy and lower toxicity.

Finally, MTTs are administered at a fixed dose that is not adjusted based on body weight or body surface area. Although the relevance of such adjustments is debatable and has been a matter of intense controversy, fixed-dose administration may introduce a higher interpatient variability that has to be taken into account in the management of MTTs.

H&O What are the problems with the current DLT assessment system?

SPV The current drug development system has several problems. First, late toxicities (ie, toxicities occurring after cycle 1) often are not taken into account in the dose recommendation process. Second, prolonged moderate toxicities that can severely impact the patient's quality of life and lead to dose reduction or drug discontinuation are inconsistently considered to be DLTs, and almost never are reported in phase 1 trial manuscripts. Third, the drug development process needs to remain as cost-effective as possible, meaning an accurate and rapid determination of the recommended phase 2 dose with the inclusion of a minimal number of patients into the dose escalation phase. In this context, the assessment and introduction of novel or unusual phase 1 designs is more challenging. Fourth, because most drugs now display very promising activity as early as the phase 1 dose escalation period, dose expansion cohorts tend to mostly focus on patient selection and search for activity. Although this is fully legitimate and laudable, it is sometimes forgotten that the primary objective of phase 1 clinical trials is to determine the optimal dose to be administered in later-phase clinical trials, and that expansion cohorts also should focus on fine-tuning the assessment of the recommended phase 2 dose.

H&O How serious are these problems? What are the outcomes?

SPV These problems currently are impacting the drug development of several MTTs and immune checkpoint modulators. This is well illustrated by a very interesting review by Fontes Jardim and colleagues that was published in *Clinical Cancer Research* in 2013, which reported that the ability to predict the future registered dose of a drug was worse for phase 1 clinical trials evaluating MTTs than for phase 1 clinical trials evaluating conventional cytotoxic agents.

One interesting example is ceritinib (Zykadia, Novartis). After the phase 1 trial, which focused on activity and patient selection during the expansion cohort, a dose of 750 mg once daily was recommended and approved by the US Food and Drug Administration (FDA). However, FDA reviewers were concerned about the drug's gastrointestinal tolerability. Because a positive food effect was demonstrated for this drug, they recommended a posteriori the investigation of lower doses taken with a meal, in order to limit the drug's toxicity without altering its effectiveness.

Additional special challenges occur when using immune checkpoint modulators, because the MTD is usually not reached and the optimal schedule of administration is unknown. This results in the exploration of multiple doses and administration schedules in later-phase

clinical trials, which multiplies the cost of drug development and complicates the final dose recommendation.

H&O Can you describe some studies that highlight the need for change?

SPV Two comprehensive studies currently evidence this need for change. Both studies were aimed at thoroughly describing all drug-related toxicities that occurred in phase 1 clinical trials of MTTs by recording all grades of toxicity and all cycles of occurrence. In the initial pilot retrospective study, published in 2011 in the *Journal of Clinical Oncology*, we analyzed more than 2500 toxicities that occurred in 445 patients enrolled in 36 eligible clinical trials, evaluating MTTs at the Royal Marsden Hospital (London, United Kingdom) and at the Institut Gustave Roussy (Villejuif, France). Strikingly, more than 50% of the severe toxicities occurred after cycle 1, and more than 50% of the patients presented with their worst-grade toxicity after cycle 1. Though this obviously is relevant to the choice of dose regimen, this large group of "delayed" severe toxicities would not have been included in the current definition of DLT.

In order to confirm these results, we performed another study, published in 2014 in the *European Journal of Cancer*. Through the European Organisation for Research and Treatment of Cancer (EORTC)-led initiative called DLT-TARGETT (Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted Therapies), we retrospectively collected complete drug-related toxicity data from 54 phase 1 clinical trials evaluating MTTs, representing almost 25,000 toxic events. This study focused on cycle 1 to cycle 6, as the quasi-totality of toxicities was observed within this period in the pilot study. This very large-scale study not only confirmed results from the initial study, but also revealed that 15% to 20% of patients received less than 75% of the intended relative dose intensity (ie, the ratio of the dose that patients effectively received and the dose that patients theoretically should have received in the absence of dose reduction and dose modification) at any time during the trial. Moreover, some specific toxicities (including life-impacting toxicities such as fatigue) occurred mainly at later cycles, and were rarely detected at cycle 1.

H&O What changes were recommended based on this study?

SPV The recommendations that we made through the DLT-TARGETT task force, based on the results of this study, are as follows: (1) take into account all available information in the dose-increment recommendation, in particular DLTs observed beyond cycle 1 at any prior dose

level, or any other drug-related toxicity leading to a treatment interruption or a dose reduction; (2) exhaustively report all toxicities in phase 1 trial manuscripts, including all grades and cycles of occurrence, and thoroughly assess their causality, as this will be key for the dose recommendation process; (3) focus the dose expansion cohort(s) on fine-tuning the dose-finding process, and make sure that searching for activity is a secondary objective; and (4) recommend the dose for later clinical trials based on achieving more than 75% of the relative dose intensity.

We did not recommend expanding the duration of the DLT period used for dose escalation beyond cycle 1, so that phase 1 clinical trials will still be cost-effective and the drug development process will not be not delayed, allowing patients to have access to effective drugs as early as possible. Consequently, dose escalation timing still would be based on toxicity data emerging from cycle 1 only.

H&O Are experts updating the way they determine and use DLTs?

SPV Yes, experts currently are acknowledging the need to reestablish the definition of DLT, as shown by the results of a very interesting international survey that was performed recently. Among 65 expert phase 1 investigators surveyed, 4 out of 5 suggested extending the DLT assessment period, with the provision not to delay patient accrual. Furthermore, most suggested updating the DLT definition to include significant decreases (<70%) in the intended relative dose intensity. Interestingly, although

moderate (grade 2) or even mild (grade 1) toxicities that could be included in this new DLT definition varied among investigators, physicians mostly feared irreversible toxicities, toxicities for which no efficacious medical treatment was currently available, and toxicities strongly impacting the quality of life (eg, ocular toxicities, cardiac toxicities, gastrointestinal toxicities, neurologic toxicities, and fatigue).

Suggested Readings

Fontes Jardim DL, Hess KR, Lorusso PM, et al. Predictive value of phase I trials for safety in later trials and final approved dose: analysis of 61 approved cancer drugs. *Clin Cancer Res*. 2013;20(2):281-288.

Le Tourneau C, Razak AR, Gan HK, et al. Heterogeneity in the definition of dose-limiting toxicity in phase I cancer clinical trials of molecularly targeted agents: a review of the literature. *Eur J Cancer*. 2011;47(10):1468-1475.

Paoletti X, Le Tourneau C, Verweij J, et al. Defining dose-limiting toxicity for phase 1 trials of molecularly targeted agents: results of a DLT-TARGETT international survey. *Eur J Cancer*. 2014;50(12):2050-2056.

Postel-Vinay S, Gomez-Roca C, Molife LR, et al. Phase I trials of molecularly targeted agents: should we pay more attention to late toxicities? *J Clin Oncol*. 2011;29(13):1728-1735.

Postel-Vinay S, Collette L, Paoletti X, et al. Towards new methods for the determination of dose limiting toxicities and the assessment of the recommended dose for further studies of molecularly targeted agents—Dose-Limiting Toxicity and Toxicity Assessment Recommendation Group for Early Trials of Targeted Therapies, an European Organisation for Research and Treatment of Cancer-led study. *Eur J Cancer*. 2014;50(12):2040-2049.

Ratain MJ. Redefining the primary objective of phase I oncology trials [published online September 9, 2014]. *Nat Rev Clin Oncol*. doi:10.1038/nrclinonc.2014.157.

Soria JC. Phase 1 trials of molecular targeted therapies: are we evaluating toxicities properly? *Eur J Cancer*. 2011;47(10):1443-1445.

Topalian SL, Hodi FS, Brahmer JR, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. *N Engl J Med*. 2012;366(26):2443-2454.