Finding the Right Dose for Cancer Therapeutics—Can We Do Better?

Eric H. Rubin and Keaven M. Anderson

Unlike other diseases, dose-selection for cancer therapeutics is often based on the maximum-tolerated dose in phase 1 studies involving relatively few patients. In this issue of Clinical Cancer Research, Jain and colleagues provide evidence that lower doses may be as effective as maximum-tolerated doses in the treatment of cancer patients. Clin Cancer Res; 16(4); 1085–7. ©2010 AACR.

In this issue of Clinical Cancer Research, Jain and colleagues (1) report an analysis of a selection of phase 1 trials at MD Anderson Cancer Center, investigating differences in clinical outcomes as a function of dose, in which patients were categorized as having been treated at low dose [≤25% maximum-tolerated dose (MTD)], medium dose (25–75% MTD), or high dose (≥75% MTD). The results indicate that time to treatment failure and response within 3 to 12 months after starting the trial were similar in patients treated at low, medium, and high dose levels. The relatively large number of patients is notable, and although the trials were a mixture of single-agent and multi-agent studies, patient characteristics were similar among the high, medium, and low dose groups. Although the results from this retrospective analysis must be interpreted with caution, they clearly suggest that “more” is not necessarily “better” when selecting doses for cancer therapeutics.

A major goal of oncology phase 1 trials is to identify the MTD, which is often selected as the dose for subsequent studies [i.e., the recommended phase 2 dose (RPTD)]. However, it is not uncommon for an MTD established in a phase 1 trial to be poorly tolerated in subsequent phase 2 and 3 trials. Among the explanations for this phenomenon are the following: (1) relatively small numbers of patients are treated in phase 1 trials at any given dose; (2) commonly used dose-finding algorithms such as the “3+3, up and down method” perform relatively poorly in terms of identifying a dose associated with a specific toxicity rate; (3) dose finding is based only on toxicities that occur during the first cycle of therapy. Notably, depending upon the relationships between dose-response curves for anticancer activity and toxicity for a given compound, the MTD may be higher than necessary for maximal anticancer activity, resulting in exposure of patients to increased toxicity without an increase in efficacy (Fig. 1).

It is important to recognize that outside of oncology, selection of a RPTD is typically not based on an MTD, but on target engagement through a surrogate endpoint. Indeed, when cancer is viewed as a chronic illness, selection of the optimal dose can be viewed in the context of the approach used in chronic, nonmalignant diseases. Typically, greater attention is paid to dose-finding in patients with these diseases than in cancer patients. This approach generally requires strong evidence of a robust surrogate marker that is likely to reflect clinical benefit. Although this has been successful in some diseases (e.g., viral load as a surrogate endpoint for AIDS trials), surrogates have mixed history of success in other diseases, including cancer (2). In any case, a minimum effective dose (MED) is often sought as opposed to an MTD. The study by Jain and colleagues suggests that the MED approach may be worth considering for cancer therapeutics, particularly in the era of targeted therapies.

Although the analysis by Jain and colleagues is provocative, there are several caveats that must be considered. First, the inclusion of “stable disease” in calculation of a “benefit rate” can be questioned, because a stable disease outcome may reflect a slow tumor growth rate rather than a drug effect. Response Evaluation Criteria in Solid Tumors (RECIST) analyses of tumor measurements on computed tomography (CT) scans are commonly used to assess complete and “partial response” in phase 1 studies (3). Using RECIST, which involves one-dimensional analyses of tumor size, complete and partial response rates are typically very low in phase 1 trials—a fact not noted by Jain and colleagues. Because nearly half of oncology compounds fail to show clinical benefit even in phase 3 trials (4), a pessimistic view of any set of phase 1 trials is that, on average, there is little efficacy at any dose. However, use of volumetric analyses of radiographic images or more advanced imaging techniques (5–7) may improve both accuracy and efficiency of detection of clinically meaningful differences in treatments (including differences related to high versus low doses.

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Measurement of tumor size as a continuous variable, as opposed to the relatively blunt RECIST categorical outcomes based on one-dimensional measurements, may also improve detection of active versus inactive compounds (or doses; ref. 8). With uniform application of volumetric imaging, a future version of the study by Jain and colleagues could be more conclusive about efficacy.

Assuming that a non-MTD dose might be preferred for a given anticancer compound, how should this dose be identified? Useful approaches include evaluation of pharmacokinetic and pharmacodynamic endpoints that can be correlated with efficacy on the basis of preclinical models. For example, use of studies designed specifically to assess pharmacodynamic endpoints (often referred to as “phase 0” studies) may improve confidence that meaningful target engagement has been achieved for a given dose and schedule of administration (9). Nevertheless, the validity of preclinical models for clinical dose selection is often questionable, and thus randomized trials that assess both tumor reduction and toxicity as a function of dose are often preferred. An example of this approach involves temsirolimus, which targets the mammalian target of rapamycin (mTOR) pathway. A phase 2 trial was designed to compare three different dose levels in a randomized manner: 25, 75, or 250 mg administered as a weekly intravenous infusion (10). Although not formally designed to compare outcomes between dose levels, with 30 assessable patients per arm and assuming a true response rate of 15%, there was 95% power to exclude a response rate of 0.8% from the 95% confidence interval for each arm. Assuming a 15% dropout rate, the trial was designed to accrue 111 patients. Based on World Health Organization (WHO) criteria for response, the resulting response rates were 5.6, 7.9, and 8.1%, and the median time to tumor progression 6.3, 6.7, and 5.2 months for the 25-, 75-, and 250-mg dose levels, respectively. There were no statistically significant differences between dose groups in the percentages of patients who had grade 1 to 4, or grade 3 to 4 adverse events. However, the median number of doses administered was highest for the 25-mg dose, because of, in part, more frequent dose holding due to toxicity in patients receiving the higher dose levels. On the basis of the results of this study, the sponsor chose 25 mg (a non-MTD dose) as the dose for a pivotal study in renal cell cancer, which was successful.

Adaptive designs have also been used in phase 1 dose-finding studies and may improve the efficiency and/or accuracy of this process (11). In addition, attention to individual genetic variation in tumor or normal tissue may improve selection of dose for specific populations of patients. Overall, greater attention to “getting the dose right” before embarking on pivotal trials or allowing multiple doses in pivotal trials should improve the success rates of these trials for cancer therapeutics.

Disclosure of Potential Conflicts of Interest


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