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Commentary: Tumor Growth, Patient Survival, and the Search for the Optimal Phase II Efficacy Endpoint

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One of the gross deficiencies in modern oncology research is the oversimplification of cancer biology in an attempt to streamline the analysis and interpretation of clinical trials. One highly simplified metric in common clinical use in phase II trials is the objective response rate, which reduces the complex interaction of an anticancer agent and tumor biology into a bivariate (yes or no) outcome parameter. Nearly all clinical investigators can apply simple tumor response criteria, such as the Response Evaluation Criteria In Solid Tumors [1] or the World Health Organization response guidelines [2] to two-dimensional clinical imaging technologies with relative ease. However, the reduction of human tumor growth dynamics into a simplistic categorical variable risks ignoring a substantial quantity of clinically important data. Historically, the evaluation of cytotoxic chemotherapeutic agents using traditional response rate criteria has had modest utility in selecting agents with sufficient antitumor activity for further clinical development. More recently, the high failure rates in later stage oncology trials compared with other therapeutic areas [3] have engendered substantial criticism [4]. Modern day skeptics in this age of targeted therapies have characterized our reliance on traditional phase II response rates as being woefully inadequate [5].

But what are the alternatives for the initial evaluation of the antitumor efficacy of a new therapeutic agent? One option is to ignore tumor volume changes, and instead evaluate nontraditional endpoints such as time to tumor progression, or the progression-free survival interval. However, such parameters are highly dependent on the population under study and may not be well suited for initial readouts of antitumor activity in early phase II trials. Other metrics that maintain a focus on tumor volume include the creation of a disease control parameter (stable disease plus partial response plus complete response rates) or the use of a continuous endpoint based upon the absolute change in tumor size. This latter method has been well described by Karrison and colleagues [6], and its representation in graphical form is the increasingly popular waterfall plot. However, even this sophisticated approach fails to use the full complement of tumor growth data collected over the entire time of monitoring in a clinical trial.

Obviously, the real world of tumor biology is highly complex. A growing human tumor can respond to pharmacological intervention in a variety of ways. For example, a tumor can continue to grow at the same rate despite the introduction of a novel treatment, or it can slow its rate of growth.
growth but still increase over time. Alternatively, it can stabilize with apparent zero growth, or it can regress via a negative growth rate in response to treatment. Finally, a combination of these responses may be observed at different times in the presence of continued treatment. By definition, in the absence of curative or indefinitely active cytostatic therapy, all tumors will resume growing eventually. How then to capture this complexity in a clinically useful manner?

Stein and colleagues, in this issue of The Oncologist, have proposed a novel approach to this dilemma [7]. They used a straightforward mathematical model for tumor growth, which includes both a growth and a regression rate parameter. Prostate-specific antigen (PSA) measurements from androgen-independent prostate cancer patients treated with an experimental anticancer agent were modeled using this approach, and the fitted growth parameters for each patient were correlated with clinical outcomes. Overall survival was more strongly correlated with the logarithm of the growth rate constant than with the regression rate. They concluded that the critical determinant of survival is whether or not a therapy alters the inherent growth rate of the tumor. Thus, modeling tumor growth during experimental treatment may be an ideal way to analyze clinical trial data for an early sign of clinical benefit. This novel approach has the advantage of using the full dataset of tumor volume measurements collected during a study. It is an innovative approach, but in its current form, it is only a half-step forward.

The approach developed by Stein et al. [7] may be well suited to prostate cancer, but there are many potential problems and pitfalls that could preclude its widespread application to other solid tumors. For instance, prostate cancer has a reliable biomarker of tumor growth, the PSA level, which represents a continuous, easily accessible, and objective output variable. In contrast, standard solid tumor radiographic response criteria are more user dependent, and potential problems including measurement errors and inter-observer variability in the application of any of these guidelines are well documented [8]. Other complicating factors include the appearance of a solitary new lesion synchronous with shrinking target lesions, which complicates the use of tumor volume as a linear continuous response variable.

An even more important criticism is that there is, as yet, no prima facie evidence that the growth rate parameter in prostate cancer patients during treatment is a useful predictive endpoint for treatment-induced benefit. In this single-arm, observational study, the tumor growth rate correlation with overall survival may represent a simple prognostic factor reflecting the underlying natural history of the tumor, independent of any modest treatment effect. It is a fact that patients with fast-growing tumors have poor survival outcomes. What is still unproven is whether a treatment-related change in the tumor growth rate parameter corresponds to a treatment-induced change in survival. The absence of a control arm precludes making any definitive conclusions. Full validation will likely require data from a randomized controlled study demonstrating that treatment-related change in the tumor growth rate parameter results in a treatment-related change in survival. An analysis of this type should be the next study undertaken by these investigators.

Because of these limitations, the novel approach suggested by Stein et al. [7] is not quite ready for prime time. Nonetheless, this strategy is interesting, and should be evaluated further in a larger population of prostate cancer patients with appropriate controls. If validated, the full application of this approach to solid tumor studies may be bolstered by the development of increasingly sophisticated three-dimensional volumetric imaging methods [9]. These computer-automated techniques have the potential to convert crude manual assessments of tumor volume into a more robust and reproducible endpoint. The complex pharmacology of molecularly targeted anticancer agents demands greater sophistication in our clinical trials. Ultimately, for patients with terminal disease, the most important endpoints are easy to define: longer survival and better quality of life. The identification of early metrics that are strongly predictive for these clinical outcomes would be a sentinel achievement. The novel strategies proposed by Stein and colleagues [7] that build upon the work of Karrison and others [6] are moving us in the right direction.

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