EDITORIALS

Phase I Trials: A Strategy of Ongoing Refinement

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The current processes involved in the development of antineoplastic drugs for clinical application reflect a model followed in the late 19th century by Dr. Paul Ehrlich in producing his "magic bullet" for the treatment of syphilis. These processes include recognition of some target to exploit in neoplastic cells or, more likely, the demonstration that a compound has in vitro activity in some model tumor system; structural elucidation of the compound; in vivo testing for activity and toxic effects; and clinical trials to evaluate toxic effects and to define an appropriate dosage for use in trials defining antineoplastic activity. Not infrequently, associated efforts, again following the model of Ehrlich, involve chemical synthesis of analogues of the index or lead compound, with the aim of producing a compound suitable for clinical testing or one with an enhanced therapeutic index. With time, each of these aspects of antineoplastic drug development has been refined as a result of new technical developments or the development of new conceptual approaches evolving from prior accrued experience. Implicit in these strategies is the desire to produce the most fruitful search, the most efficient preclinical process, and a clinical evaluation of agents that treats the fewest patients with suboptimal doses yet minimizes the risk of drug-related morbidity and mortality. One of the novel concepts that has received much attention is the use of drug "blood levels" associated with preclinical toxic effects as a basis for dosage escalation in clinical trials of that agent (1,2). Inherent in this strategy is that a pharmacokinetic-pharmacodynamic relationship exists, i.e., that drug concentrations in the plasma reflect concentrations of drug at its eventual site of action, and that drug effect is related to those concentrations.

The study by Gianni and co-workers published in this issue of the journal (3) is an elegant example of the application of this concept to an analogue of doxorubicin. The study, as published, is notable for a number of aspects. It clearly illustrates the point that there will always be exceptions to a rule and that such examples of aberrant behavior usually have a sound basis with a rationale that is frequently enlightening. In an era of spectacular technological and intellectual advances in molecular biology, the study by Gianni and co-workers is testimony to the continued importance of defining the metabolism and disposition of agents with low therapeutic indices. The recognition of the rapid and extensive conversion, in humans, of iododoxorubicin to iodo-

doxorubicinol by an enzyme not present in mice clearly demonstrates the importance of carefully defining the metabolism of an agent in vivo and characterizing the enzymology responsible for such metabolism. Without integration of these concepts and without testing the resulting hypotheses with regard to in vitro cytotoxicity versus myeloid precursors of parent compound and its primary metabolite, iododoxorubicin would have been cited as evidence against the usefulness of pharmacokinetically guided dose escalation. As the concept of blood level-based dose escalation is developed, issues such as species differences in drug metabolism or plasma protein binding will continue to appear as issues to be included in further refinement of the overall strategy.

Another concept that has received much recent attention and is relevant to the study by Gianni et al. (3) is the clinical pharmacokinetic-pharmacodynamic relationships of antineoplastic agents (4,5). As mentioned earlier, this is an underlying premise in the use of animal toxicology and pharmacology to guide the dosage in humans. However, humans, unlike the mice used in preclinical toxicology and pharmacology studies, are not inbred. As a result of differences in a number of variables such as genetics, nutritional status, disease state, concomitant disease conditions, and concomitant therapy, substantial interpatient differences occur in drug metabolism and disposition. These differences manifest themselves as substantial variations in drug exposure within cohorts of patients, all of whom received the same dosage of drug. Consistent with these principles, Gianni and colleagues have provided evidence that, in their patients, there is a better relationship between myelosuppression and the areas under the curves of iododoxorubicin and metabolite than between myelosuppression and drug dose. This is not surprising.

It would be more desirable for such an analysis to be refined somewhat further. This could be done initially by considering each patient's pretreatment white blood cell (WBC) count or neutrophil count. Such a modification would take into consideration the interpatient variation in pretreatment leukocyte status, which is as quantitatively important as the variation in drug disposition. More specifically, a reduction in leukocyte counts or neutrophil counts to 1,000/μL in a patient with pretreatment counts of 10,000/μL would conceptually reflect or require more drug effect than it would to produce the same WBC count nadir in a patient with a pretreatment WBC count of 4,000/μL. This concept of percentage reduction in myeloid elements or, viewed another way, survival fraction has proven applicable in a variety of other studies of antitumor agents including some antitumor agents (4). Another attraction of such an analysis would be its correspondence to the in vitro data in the current study wherein the effects of iododoxorubicin and iododoxorubicinol on myeloid precursors were expressed as percentage survival compared to untreated controls.

A subsequent logical refinement in relating the pharmacokinetics of iododoxorubicin and iododoxorubicinol to the pharmacodynamic consequences of therapy would be to use something other than a linear model to relate drug exposure to myelosuppres-
By definition, the pretreatment WBC count and the fact that a WBC count nadir cannot be less than zero put upper and lower limits on the range of absolute leukopenia or percentage reduction that can be produced by any drug exposure. The use of exponential relationships and modified Hill's equations has proven quite suitable in this regard for anthracyclines as well as for other antineoplastic agents (4). Under ideal circumstances, one could even envision a situation in which such defined relationships could produce further refinement in clinical dose escalation schemes, whereby the quantitative relationships between in vitro exposure to a drug and the inhibition of myeloid precursors could be incorporated into the scheme that would target plasma drug exposure.

It would be fascinating to extend the study by Gianni and co-workers to a series of anthracycline antibiotics. Clinical data relating pharmacokinetics and pharmacodynamics have been published for menogaril and doxorubicin and probably exist in the repositories of other institutions that performed phase I trials of other agents such as epirubicin and idarubicin. Definition of the in vitro myelosuppressive effects of these agents might allow a unifying theme for guiding subsequent clinical development of newer anthracycline antibiotics as they are developed and might serve as a model for other classes of myelosuppressive agents.

References