Editorial

Why Drugs Fail: Of Mice and Men Revisited

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Of the large number of promising anticancer agents entering into clinical testing, only a disappointingly small number ultimately assume a place in the armamentarium of the practicing oncologist as clinically useful therapies. Thus, despite the obligatory requirement for showing promising activity in preclinical models, only a select few new drugs will successfully traverse the hurdles necessary to demonstrate both clinical safety and efficacy that are required for approval by regulatory agencies. This stark reality is the fundamental challenge of clinical cancer drug development.

In the area of anticancer developmental therapeutics, the most commonly used preclinical model system for efficacy testing is the human tumor xenograft growing in immunodeficient nude mice. All too often, discrepancies between impressive activity in human xenografts and the disappointing lack of efficacy in subsequent clinical trials has led to a loss of confidence in, and expanded criticism of, our preclinical testing systems. The ramifications of a potential disconnection between preclinical and clinical testing can affect the entire field of medical oncology. It is not uncommon for promising preclinical laboratory animal tests to be misinterpreted by a well-intentioned lay press, leading to overly optimistic expectations and demands for widespread access to as yet unproven treatments in early clinical trials. These reports can also greatly impact the general public, including government legislators, financial investors, and, most importantly, cancer patients and their concerned families. The potential exists for a damaging backlash. One important solution is to better educate the general public about the orderly steps necessary for rational drug development. But a second complementary answer suggested by Kirsten et al. (1) in this issue of the journal is to improve our understanding of how existing preclinical models can be rationally applied to clinical drug development.

In many ways, 9-AC is an excellent example of the all too common situation where a new drug with high preclinical expectations ultimately fails to show any meaningful clinical activity. In 1989, Giovanella et al. (2) published their impressive preclinical studies of 9-AC in Science, showing the curative potential of this agent in nude mice bearing established human colon cancer xenografts. Subsequently, the antitumor activity of 9-AC was also described in a broad variety of different human tumors (3, 4), leading the National Cancer Institute in 1992 to designate 9-AC as a high priority compound for further clinical development. Further motivation came from the ongoing successful development of two other camptothecin derivatives, topotecan and irinotecan, that were both eventually approved for clinical use by the Food and Drug Administration in 1996. Phase I trials of a 72-h infusions of 9-AC were initiated in 1993 and demonstrated predictable dose-dependent myelosuppression as its major toxicity (5, 6). However, in subsequent Phase II trials, despite showing modest activity in ovarian cancer (7) and malignant lymphoma (8), the drug was not found to be active against lung cancer (9) or colon cancer (10) on any schedule. Thus, in contrast to its camptothecin brethren, irinotecan and topotecan, 9-AC was dropped from further drug development in 1999. The impressive preclinical activity of 9-AC was ascribed to limitations inherent in preclinical animal testing.

But Kirsten et al. (1) suggest that this may be an overly simplistic answer. Valuable lessons may be learned from our experience with 9-AC that can help to make better informed decisions about developing future agents in this same class of drugs. By carefully comparing 9-AC pharmacokinetics and pharmacodynamics in preclinical animal efficacy experiments to similar studies in early clinical trials, some logical findings emerged that potentially explained the failure of 9-AC to demonstrate impressive antitumor activity in humans. By extending the concept of a MEDOR of tumors (11) to include a minimally effective threshold exposure to 9-AC in plasma, a new parameter was defined that could more readily be compared across species in preclinical and clinical studies. For example, administration of 9-AC on a schedule of daily times 5 days for 2 weeks repeated every 21 days demonstrated the most optimal antitumor activity in the xenograft models of pediatric tumors. On this schedule in mice, the MEDOR defined by the corresponding cumulative area under the concentration curve ranged from 690 to 1580 ng/ml/h; however, in human clinical studies, the maximum achievable exposures to 9-AC were substantially limited by myelosuppression, ranging from 126 to 493 ng/ml/h. Thus, the greater sensitivity of humans compared with mice to the myelosuppressive effects of 9-AC precluded achieving the plasma drug exposures necessary for optimal anticancer activity. For the development of drugs, such as the camptothecins, which have relatively steep exposure-response curves and relatively narrow therapeutic indexes, decreases in overall systemic exposure can be the difference between success and failure. This retrospective analysis was ultimately borne out by the lack of meaningful clinical activity of 9-AC seen in clinical Phase II trials (9, 10). Interestingly, these observations are highly consistent with a preclinical study by Erickson-Miller et al. (12), demonstrating that mouse bone marrow progenitor cells were 6–11-fold more resistant to 9-AC than human progenitor cells.

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2The abbreviations used are: 9-AC, 9-aminocamptothecin; MEDOR, minimally effective dose for causing objective regression.
Thus, *in vitro* testing also predicted that lower plasma 9-AC exposures would be achievable in humans compared with mice because of a difference in tolerance of host tissues.

Fundamentally, this well-conceived approach espoused by Kirstein *et al.* (1) is not radical or revolutionary; rather, it is a common sense plea for performing better pharmacokinetic and pharmacodynamic studies both in preclinical experiments and in early clinical development. We should strive for more in-depth communication between preclinical and clinical scientists early in the drug development process. Some prominent drug development groups, including the authors of this article (1), who are based at St. Jude’s Children’s Research Hospital, have been highly successful in integrating preclinical and clinical anticancer drug development, as demonstrated by their related body of work with other camptothecin derivatives (13, 14). However, the field as a whole can and should be doing much more. These issues are more relevant than ever, because the monumental advances in molecular oncology and in understanding the human genome are leading to an explosion of new and novel therapeutic agents entering into the anticancer development pipeline. Our challenge as drug development scientists is to bring these scientific advances into the clinical arena as rapidly, rationally, and expeditiously as possible. Our patients and future generations of cancer patients deserve nothing less.

**References**


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