Predictive Value of Preclinical Toxicology Studies for Platinum Anticancer Drugs\textsuperscript{1,2}

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ABSTRACT

Rodent and nonrodent toxicology studies are currently expected to support Phase I trials of antineoplastic drugs in the United States. To determine the predictive value of these studies, we initiated a project to compare preclinical and clinical toxicity data within various drug classes. The first class analyzed was the platinum anticancer drugs. Twelve platinum analogues that had both preclinical (mouse, rat, and/or dog) and clinical data from matching drug administration schedules were identified. The rodent LD\textsubscript{10} (the dose that causes lethality in 10\% of treated animals) or dog toxic dose high (a dose that when doubled causes lethality in dogs) correlated well with the human maximally tolerated dose high (a dose that when doubled causes lethality in 10\% of treated animals) or dog toxic dose high in mg/m\textsuperscript{2} basis. For every platinum analogue investigated, one-third the rodent LD\textsubscript{10} or one-third the dog toxic dose high gave a starting dose and a first escalation dose that did not exceed the clinical maximally tolerated dose. The dose-limiting toxicities in patients were previously observed in 7 of 7, 7 of 8, and 9 of 11 mouse, rat, and dog studies, respectively. Our data indicate that mice, rats, and dogs all had value in predicting a safe starting dose and the qualitative toxicities in humans for platinum anticancer compounds. The efficiency of Phase I trials could have been improved without sacrificing patient safety by allowing higher starting doses for this drug class than conventionally permitted.

INTRODUCTION

The goals of preclinical toxicology studies for oncology drugs are: (a) to identify a starting dose that is both safe and that minimizes the number of patients treated with ineffective doses; (b) to identify important potential clinical toxicities; and (c) to assist in the design of human dosing regimens and escalation schemes (1). Since 1982, both rodent and nonrodent toxicology studies have been requested to support Phase I trials of antineoplastic drugs conducted under an IND\textsuperscript{4} in the United States (2, 3). In contrast, rodent toxicology studies alone can support initial clinical trials of antineoplastic drugs conducted under the auspices of the EORTC and CRC (4). The EORTC and CRC have documented their experience with this approach (5, 6). The approach initially promulgated by the NCI (2, 3) and adopted by the FDA has not been extensively examined.

The FDA has one of the largest collections of preclinical and clinical data for investigational and marketed antitumor drugs. We have begun to analyze this data and the biomedical literature for the value of preclinical toxicology studies in predicting the MTD and end-organ toxicities in humans. Due to the quantity of the drugs and associated data available for analysis, we began by evaluating the data for a single drug class, the platinum anticancer drugs. We determined the predictive value of the rodent (mouse or rat) LD\textsubscript{10} or dog TDH (a dose that when doubled causes lethality in dogs) for estimating a safe starting dose in humans and compared the major toxicities reported in experimental species and humans. From our analyses we determined that: (a) either rodents or dogs may be used to safely predict the starting doses of platinum drugs in humans, but mice were less accurate than rats and dogs; (b) calculation of the starting dose based on one-tenth the rodent LD\textsubscript{10} may be too conservative for platinum anticancer drugs; and (c) rodents and dogs were equally predictive of DLTs in humans.

MATERIALS AND METHODS

Data were collected for 12 platinum analogues (cisplatin, carboplatin, tetraplatin, iroplatin, CI-973, enolplatin, JM216, \textsuperscript{1-NDPP}, lobaplatin, oxaliplatin, spiroplatin, and zeniplatin) for which Phase I results were available (Table 1). Data were garnered either from the biomedical literature or from studies supporting INDs submitted to the FDA (7–18). Only preclinical or clinical studies with drug administration schedules of either single dose or once daily for 5 days (daily or clinical) were analyzed. LD\textsubscript{10\%} were determined by Probit analysis or, if insufficient data were available for a Probit calculation, as the dose that actually caused 10\% lethality. If an LD\textsubscript{10} was not available by either of these approaches, then the LD\textsubscript{10} was taken as the highest non-

\textsuperscript{1} Supported in part by Review Science Research Award RSR-003A from the Center for Drug Evaluation and Research, Food and Drug Administration.

\textsuperscript{2} This article is not an official Food and Drug Administration guidance or policy statement. No official support or endorsement by the Food and Drug Administration is intended or should be inferred.

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\textsuperscript{4} The abbreviations used are: IND, investigational new drug application; EORTC, European Organization for Research and Treatment of Cancer; CRC, Cancer Research Campaign; NCI, National Cancer Institute; FDA, Food and Drug Administration; MTD, maximally tolerated dose; LD\textsubscript{10}, dose that causes lethality in 10\% of treated animals; TDH, toxic dose high; DLT, dose-limiting toxicity; AUC, area under the curve.

Received 8/17/98; revised 2/8/99; accepted 2/8/99.

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lethal dose. Eleven of the twelve drugs were administered i.v. in all species and the remaining drug was administered p.o. All of the twelve platinum analogues investigated were administered in the single-dose schedule, whereas five were also administered once daily for 5 days. Thus, a total of seventeen pairs of preclinical and clinical datasets could be analyzed for quantitative dose comparisons. Single dose data for one drug were excluded from quantitative comparison because Phase I trials were terminated before an accurate MTD was reached.

The capability of mouse, rat, or dog studies to predict qualitative toxicities observed in humans was also examined. The occurrence of DLTs and non-DLTs in humans was tabulated and compared with preclinical findings. Included in our analysis are toxicities that were evident from clinical, laboratory, and histopathological findings. The absence of a preclinical finding may have resulted from the design of the study rather than its true absence (e.g., no serum chemistry was performed that might have detected renal toxicity). We also determined whether a toxicity was observed preclinically, but not in humans. Mouse end-organ toxicity data were available for 7 of the 12 drugs on the single-dose schedule and 3 of the daily × 5 administered drugs for a total of 10 drug schedules. Rat end-organ toxicity findings were available for 10 drug schedules: 8 from the single-dose administration schedule and 2 from the daily × 5 schedule. Dog end-organ toxicity were available for 11 of the single-dose schedule drugs and 4 of the drugs administered on the daily × 5 schedule for a total of 15 drug schedules. Preclinical end-organ toxicity data in three experimental species were available for three drugs. With one exception, all preclinical studies that were performed with the daily × 5 schedule were also performed with the single-dose schedule.

All preclinical doses were normalized to mg/m². LD₁₀ values reported in mg/kg in mice and rats were multiplied by 3 and 6, respectively, and the dog MTD values were multiplied by 20 to convert from mg/kg to mg/m² (19). The MTD values used in the analysis were defined and reported by the investigators and, thus, may be above or equal to the recommended Phase II dose. When the preclinical or clinical studies provided equivocal results, final values were chosen while blinded to the corresponding animal or human value.

Consistent with current conventions, the starting dose was defined either as one-tenth the rodent LD₁₀ or one-sixth the dog TDH after doses were normalized by mg/m² (1). Linear regressions were calculated using Sigma Plot (SPSS, Inc., Chicago, IL). Descriptive statistics and hypothesis testing were performed with the Excel spreadsheet program (Microsoft Corp., Redmond, WA) and Statistical Analysis Software (SAS Institute, Cary, NC).

For determining the efficiency of the Phase I trials, the number of modified Fibonacci dose levels required to reach MTDs from the starting dose was calculated. The starting dose for this calculation was determined according to current practice and may not reflect the actual starting dose. Likewise, the actual escalation scheme and, therefore, the number of dose levels needed to reach the MTD may have differed from this hypothetical model.

To determine the probability that a starting dose for a new platinum drug chosen from the most sensitive rodent would be at or above the clinical MTD, a linear regression analysis using the available platinum drug dataset was performed with human MTD in mg/m² as the dependent variable and the LD₁₀ in mg/m² from the most sensitive rodent for each drug as the independent variable. The sample sizes of the most sensitive rodent LD₁₀ determinations were reflected as relative weights in this regression. For three drugs, the sample sizes were unknown and they were assumed to be a minimum of 10 animals. The confidence intervals within the range of predicted MTD values were calculated. Under standard regression assumptions, the predicted MTDs were normally distributed. The probability of starting at or above the MTD, using either one-third or one-tenth the LD₁₀ from the most sensitive rodent as the starting dose, was determined as the area under the normal curve below the MTD.

**RESULTS**

**MTD:LD₁₀ and MTD:TDH Ratios.** The ratio of the human MTD to the rodent LD₁₀ or dog TDH was determined for each drug schedule. The ratio indicates whether the preclinical results under- or overpredicted the human MTD. The ratios for the single-dose schedule are shown in Fig. 1A. In general, the human MTDs were underpredicted for these platinum drugs. The mean ratios ± SE were 2.36 ± 0.33, 1.74 ± 0.24, and

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1.67 ± 0.17 for the mouse, rat, and dog, respectively. These means were not significantly different from each other (ANOVA, \( P > 0.05 \)). All of the ratios were >1, except for a single drug in both the mouse and dog and a second drug in the rat.

There were far fewer LD\(_{10}\) and TDH determinations in the daily \( \times 5 \) schedule. With this schedule of administration, LD\(_{10}\) or TDH values were determined for only four, three, and four drugs in mice, rats, and dogs, respectively (Table 1). Two drugs had daily \( \times 5 \) LD\(_{10}\) determinations in mice and rats, as well as a TDH determination in dogs. For these drugs, the ratios of MTD to LD\(_{10}\) largely agreed between the two rodents (0.43 versus 0.44 and 1.11 versus 0.88), but the ratios of MTD to TDH (2.00 and 0.56) were markedly different from the ratios from the rodent studies (Fig. 18). In contrast, with a third drug, the MTD to dog TDH ratio was similar to the MTD to mouse LD\(_{10}\) ratio (1.04 and 1.11, respectively).

Of the eight drugs that had LD\(_{10}\) determinations in both mice and rats in the single-dose schedule, seven drugs have lower LD\(_{10}\) values in mice (ranging from 41–80% of the rat values; Fig. 2A). Nine drugs had LD\(_{10}\) determinations in at least

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**Fig. 1** Ratio of human MTD to either rodent LD\(_{10}\) or dog TDH for platinum anticancer drugs administered on a single-dose schedule (A) or a daily \( \times 5 \) schedule (B). Doses were normalized to mg/m\(^2\) before comparison. For drugs with values above the dashed line, the animal result underpredicted the human MTD. A and B, each symbol corresponds to the same drug in all three species.

**Fig. 2** Correlation between animal estimates of MTD for a single-dose schedule. Comparison of mouse and rat LD\(_{10}\) values (A) or the most sensitive rodent LD\(_{10}\) and dog TDH (B). Dashed line, the line of unity.
one rodent, plus a TDH determination from dog studies. Every TDH value was higher than the corresponding most sensitive rodent LD$_{10}$ value (Fig. 2B), showing that dogs were less sensitive than rodents to these platinum anticancer drugs.

**Starting Dose Determinations.** Starting doses for Phase I trials in anticancer agents are generally determined from one-tenth the rodent LD$_{10}$ unless that dose is severely toxic to nonrodents. In that case, one-third the dog TDL value is used as the starting dose (1). TDH values are generally twice the TDL value, therefore, the starting dose may also be determined from one-sixth the TDH (1). Alternatively, the data available for platinum anticancer drugs suggests that selecting one-third the TDH for dogs or one-third the LD$_{10}$ for the most sensitive rodent species for the starting dose would have permitted both safe and efficient Phase I trials if using a modified Fibonacci dose-escalation scheme. For the single-dose schedule, using one-third of the LD$_{10}$ of the most sensitive rodent species for the starting dose would have allowed the MTD to be reached in an average of 4.4 fewer dose levels than if the starting dose was chosen using the conventional method of one-tenth the rodent LD$_{10}$ (Table 2). The higher starting dose would have still allowed a reasonable degree of safety because a minimum of two additional dose levels would have been evaluated before reaching the MTD. Similarly, using one-third the dog TDH as the starting dose would have resulted in an average of 2.6 fewer dose levels to reach the MTD than a starting dose of one-sixth the TDH. Patient safety is unlikely to be jeopardized if one-third the LD$_{10}$ from the most sensitive rodent is used as a starting dose for a new platinum drug similar to the 12 drugs reported here. On the basis of a linear regression analysis of this dataset, the probability of starting at or above the MTD approaches zero when using one-tenth the most sensitive rodent LD$_{10}$ as the starting dose. If one-third the most sensitive rodent LD$_{10}$ is used as the starting dose, then the probability increases to only 0.0002%.

**Correlating Preclinical Studies with the MTD.** The human MTD was plotted versus the rodent LD$_{10}$ and dog TDH values to determine the collective correlation of the data (Fig. 3, A and B). After logarithmic transformation, the correlation coefficients ($r^2$) of the linear regression lines were determined. The correlation coefficient for single-dose studies was 0.800, 0.800, and 0.840 for mouse, rat, and dog, respectively (Fig. 3A). There was, thus, no appreciable difference between the species. There was also no statistical difference in the slope of the regression line. The slopes for the single-dose administration schedule only (A) or combined single-dose and daily $\times$ 5 administration schedules (B) are shown. Mouse (——, ●), Rat (– – –, □), Dog (zzzz, ●).
were 0.874, 0.459, and 0.688 for the mouse, rat, and dog, respectively (data not shown). When the data from the single-dose and daily × 5 schedules were combined, the correlation coefficients changed slightly to 0.706, 0.843, and 0.874 for mouse, rat, and dog, respectively (Fig. 3).

Table 3  Ability of single dose administration studies in animals to predict DLTs and non-DLTs in humans

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*a Number of drugs for which toxicity was observed in humans and had corresponding animal studies performed.

Correlating Toxicity Findings. In addition to predicting the human MTD and the appropriate starting dose for Phase I trials, preclinical studies may also forecast side effects that will be encountered when the drug is administered to humans. Toxicities observed in Phase I trials of platinum anticancer drugs were predominantly hematological, gastrointestinal, renal, or neurological in origin. Importantly, the DLT (either myelosuppression, nephrotoxicity, or neurotoxicity) in this class of drugs was predicted preclinically in the majority of drug schedules (Table 3). Human DLTs were observed in 100% (7 of 7) of the relevant mouse studies, 87% (7 of 8) of the relevant rat studies, and 82% (9 of 11) of the relevant dog studies.

Every platinum anticancer drug caused myelosuppression and gastrointestinal toxicities (nausea and vomiting) when administered to patients (Table 3). The myelosuppression was manifested primarily by thrombocytopenia, but also by leukopenia and anemia. Overall, rodents (mouse and rat combined) predicted hematological toxicity in 87% (13 of 15) of the drug schedules, whereas dogs predicted myelosuppression in 82% (9 of 11) of the drug schedules. Fifty-three percent (8 of 15) of the rodent studies manifested gastrointestinal distress as diarrhea, whereas dogs exhibited either vomiting or diarrhea in 82% (9 of 11) of the studies.

It is difficult to compare nephrotoxicity between animals and humans because patients often received prophylactic measures to prevent nephrotoxicity (e.g., hydration and/or forced diuresis), whereas experimental animals may not have. Nephrotoxicity in humans, usually evident by increased blood urea nitrogen or decreased creatinine clearance, was reported for three drugs in the single-dose administration schedule. Two of the human nephrotoxic drugs had toxicity studies performed in rats, and renal damage was observed with both of them. All drugs causing human nephrotoxicity were also nephrotoxic to dogs. There were no studies in mice that assessed kidney damage for the three human nephrotoxic drugs. In addition, rats and dogs suffered renal toxicity with four and five drugs, respectively, that were not nephrotoxic to humans. Only one drug caused renal damage in all three experimental species (mice, rats, and dogs), but no nephrotoxicity was reported in humans when this drug was coadministered with mannitol to dehydrated patients. One drug caused nephrotoxicity in both schedules, whereas two drugs manifested renal toxicity only when administered on the daily × 5 schedule.

Although difficult to detect and interpret in the preclinical oncology drug development setting, neurotoxicity with platinum drugs was often predicted by the animal studies. Neurotoxicity was detected in Phase I trials of five drugs as evidenced by ataxia, tremor, or coma. Investigations in rats were performed with four of the five neurotoxic drugs. For three of these drugs, rats exhibited neurotoxicity (e.g., ptosis, ataxia, tremor, or coma). Toxicology studies in both mice and rats were performed with only one of the neurotoxic drugs. Ptosis, trembling, or seizures were observed in the mice, but not in the rats for this drug. The dog seemed to be less susceptible to measurable neurotoxicity because only one of the five drugs caused neurotoxicity (e.g., tremor, ataxia).

No hepatotoxicity has been detected in the Phase I setting with these platinum analogues despite six drugs causing elevated liver enzymes in dogs. One drug also caused hepatotoxicity in rats, but elevated liver enzymes were never reported in mice. The dog, thus, seemed to be more susceptible than humans to liver damage from these agents. Although pulmonary toxicity was never reported in humans during a Phase I trial either, pulmonary edema and hemorrhage were reported in mice and dogs for one drug, and dyspnea was reported in the rat for two.
DISCUSSION

The preclinical studies needed to support entry of oncology drugs into Phase I testing have changed considerably over the years (20, 21). Since 1982, rodent and nonrodent studies have been expected by the FDA (1–3). In contrast, the CRC and the EORTC have relied on preclinical testing of oncology drugs in rodents only (4). Grieshaber and Marsoni (2) documented the success of the current United States practice for the first seven drugs developed by the NCI under this system. The success of the rodent-only approach, as practiced in Europe, has been more extensively examined (5, 6). The drugs examined in these studies included alkylating agents, tubulin binding agents, DNA binding agents, antinecrotic agents, and others, including JM 216, a platinum anticancer agent (5, 6). For these drugs, unacceptable toxicities were never encountered at the Phase I starting dose that was determined from one-tenth the mouse LD_{10}. Although the requirement for rodent-only toxicology studies decreased the expense and time of the nonclinical development of an anticancer agent, for some drugs this approach may have led to numerous escalations in the Phase I setting (5).

To determine the value of rodent and nonrodent toxicology studies in oncology drug development, we have begun to retrospectively examine submissions to the FDA and studies in the biomedical literature. By comparing quantitative and qualitative findings between experimental species and humans, we intend to evaluate the appropriateness of current regulatory practices at the FDA. The platinum anticancer agents were the first group of drugs we examined.

Determining the starting dose for Phase I studies is a primary function of preclinical testing. In the platinum anticancer drug class, the ratios of human MTD to dog TDH seem to cluster more closely to one than the ratios of human MTD to mouse or rat LD_{10}. The mean ratios, however, were not statistically different from one another. The majority of the studies in all species underpredicted the human MTD. These data suggest that higher starting doses could have been obtained without compromising safety. Our analysis shows that if starting doses were determined from one-sixth dog TDH values, rather than from one-tenth rodent LD_{10} values, fewer dose escalations would have been required to reach the MTD. Alternatively, one-third (rather than one-tenth) the rodent LD_{10} would have also diminished the number of escalation steps required in a Phase I trial without compromising patient safety. One-third the mouse or rat LD_{10} approximated one-sixth the dog TDH for this class of drugs, so there is no clear advantage to using one method over another for determining the starting dose.

Another important function of preclinical testing is to forecast the potential toxicities that may be encountered in patients. For these platinum drugs there was no substantive difference in the value of rodents versus dogs in predicting the human toxicities, DLT or otherwise. The DLT was observed as a toxicity in 93% of rodent studies and 82% of the dog studies. Our results are consistent with those of Lelienveld et al. (22) who concluded for five platinum drugs that studies in dogs provided little new information to the data obtained in rodents.

Another factor to consider is whether the exposures (AUCs) at the preclinical and clinical MTDs were equivalent for these drugs. Perhaps, if AUCs at toxic doses rather than the administered doses were compared between species (as in Fig. 1), a different pattern of accuracy may have been observed as Collins et al. (23) have reported for three platinum anticancer agents. Such an analysis was precluded for the entire dataset, however, because plasma levels of ultrafilterable platinum were not available in more than one species for most of these drugs.

Several approaches have been proposed to optimize the efficiency of Phase I testing of oncology drugs. Simon et al. (24) recently published an analysis that supported the use of a dose-doubling escalation scheme and single-patient cohorts to more rapidly define the MTD with fewer patients. The modified continual reassessment (25) and pharmacokinetically guided (26, 27) dose-escalation methods also have been proposed to quickly escalate to the MTD. Alternatively, the time and patients needed to define the MTD could be minimized by simply beginning trials at higher doses (28, 29). The data for these platinum drugs show that starting doses could have been up to three times higher without compromising patient safety. If starting doses were determined from one-third the mouse or rat LD_{10} values, then up to four fewer hypothetical dose levels would have been needed in the initial Phase I trial using the standard escalation approach (modified Fibonacci). Whether higher starting doses are also possible for other oncology drug classes remains to be determined.

In summary, we conclude that dogs did not add any particular value to the preclinical testing of these platinum anticancer drugs. Mouse or rats revealed potential toxicities as frequently as dogs. Safe and efficient starting doses were predicted by both rodents and dogs when using current safety factors (one-tenth for rodents and one-sixth for dogs) and assuming a modified Fibonacci dose-escalation scheme. Equally safe and efficient starting doses could have been obtained by using one-third, rather than one-tenth, of the rodent LD_{10} or one-third rather than one-sixth the dog TDH. On the basis of these findings, we encourage potential sponsors of new platinum analogues to discuss with the Division of Oncology Drug Products rodent-only toxicology testing before submitting an IND to the agency.

ACKNOWLEDGMENTS

We acknowledge that data for these analyses were supplied by ASTA Medica (Hackensack, NJ), Bristol-Myers Squibb (Wallingford, CT), Lederle Laboratories (Philadelphia, PA), the NCI (Bethesda, MD), Parke-Davis Pharmaceutical Research Division (Ann Arbor, MI), Dr. Roman Perez-Soler (Houston, TX), and Sanofi Pharmaceuticals (Malvern, PA). We thank these sponsors for their gracious permission to publish their data in this format. We also thank Gary Gensinger for designing the database used to store the collected information.

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