Relationship between the Neurotoxicity of the Hypoxic Cell Radiosensitizer SR 2508 and the Pharmacokinetic Profile

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ABSTRACT

Complete pharmacological data from 71 patients treated on the phase I trial of SR 2508 were analyzed to see if the dose-limiting toxicity of peripheral neuropathy is related to the individual patient's pharmacokinetic profile. In a retrospective analysis, the risk of toxicity was best predicted by using the bivariate model of total drug exposure and the time over which the treatment course was given. Drug exposure [area under the curve (AUC)] for a single treatment was calculated by the product of the AUC times the number of drug administrations. While the clinical efficacy of hypoxic cell sensitizers remains to be proven, SR 2508 is better tolerated than its predecessors, misonidazole and desmethylmisonidazole, as three times the amount of SR 2508 can be given. If this model is confirmed in the current phase II and III trials, the probability of developing neuropathy would be predictable for an individual patient from measurements made at the time of the first drug dose, allowing for the adjustment of drug schedule to avoid all but minor toxicity.

INTRODUCTION

One of the basic principles of radiation biology is that cells irradiated under hypoxic conditions are more resistant to cell killing than cells irradiated in air. Under complete hypoxia, up to three times the dose of irradiation is required to produce as low a fraction of cell survival as that produced in air (1). It is uncertain to what extent hypoxia is important in clinical radioresistance (2, 3). Clinical trials using hyperbaric oxygen suggest that overcoming hypoxia might be useful in certain situations (2), and recent data support past observations that the local control of tumors is improved in patients with higher hemoglobin levels (4).

The clinical use of hyperbaric oxygen was cumbersome; therefore, a major effort was undertaken to develop chemical agents that would (a) sensitize hypoxic cells to irradiation; (b) diffuse into the hypoxic zones of tumors, (c) not sensitize normal tissues to irradiation; and (d) be sufficiently nontoxic so that they could be administered with many, if not all, fractions of a standard course of radiotherapy. It is important to avoid few-fraction radiation regimens in order that the effect of the best sensitizer, oxygen, be optimized. Tumors undergo a process called reoxygenation between each treatment which keeps the proportion of hypoxic cells from increasing during a course of treatment (5). Therefore, regimens with few fractions will not maximize the therapeutic gains obtained through the reoxygenation process.

The nitroimidazole compounds are electron affinic and were tested clinically as hypoxic cell sensitizers due to their potential ability to replace oxygen in the radiochemical reactions. Misonidazole, a 5-nitroimidazole compound, was the first to be tested (6). A randomized trial for patients with glioblastoma showed improved survival in patients given a nonstandard (few fraction) radiation regimen with sensitizer compared to the same radiation treatment alone. However, the median survival of the sensitizer group was no better than historical controls given standard radiotherapy, and there were no long-term survivors (7).

The 2-nitroimidazoles, having a greater electron affinity, were more efficient as sensitizers than misonidazole (8). MISO, the first drug of this class in clinical trials, produced a dose-limiting neurotoxicity such that a total dose of only 10 to 12 g/m² produced a peripheral neuropathy in about one-half the patients (9, 10). A small fraction of patients also developed central nervous system toxicity. From animal data, it was estimated that a single dose of 2 g/m² was needed to produce a sufficient sensitizing concentration of drug in tumor (11). This dose could only be given five or six times during a course of curative radiotherapy which requires 25 to 30 fractions. Most of the randomized trials showed no benefit to the use of MISO (12). Recently, however, a large randomized trial did show a statistically superior freedom from relapse and survival in patients with carcinoma of the pharynx (4).

In 1980, Brown et al. (13, 14) used pharmacokinetic principles for guidance in developing a less toxic drug. By using a less lipophilic side chain, analogues of MISO were developed that retained their electron affinity, critical to radiosensitization, while differing in their pharmacological properties. Drugs with lower lipophilicity than MISO are excluded from the central nervous system and are excreted from the body more rapidly and completely. DMM, an endogenously formed, more hydrophilic metabolite of MISO, was next used in clinical trials (15). As predicted, no central nervous system toxicity occurred with DMM. However, in terms of peripheral neuropathy, DMM was minimally less toxic than MISO with a 50% incidence of neuropathy occurring at a dose of approximately 15 g/m².

The next drug evaluated was SR 2508 (16–18). The results of the phase I trial indicate that about three times more SR 2508 can be given compared to MISO. The pharmacokinetic data presented in this report suggest that analysis of serum drug levels following a single dose of SR 2508 can predict the likelihood of a patient developing neuropathy later on in their course of treatment, thus allowing for alteration in the dose schedule to prevent this toxicity. Such a finding is of consider-
PHARMACOKINETICS AND NEUROPATHY OF SR 2508

Materials and Methods
Details of the short and long treatment schedules have been published (17, 18). The radiosensitizer phase I study differs from the usual chemotherapy phase I trial in that the end point is the maximum tolerated total dose rather than the maximum tolerated single dose. The single dose of 2 g/m² was ultimately chosen as this will produce a tumor concentration of approximately 100 µg/ml (18), a level predicted to be adequate for clinically detectable sensitization (11). A 3-week schedule was first tested to approximate the maximum tolerated total dose. Patients received three doses per week, for 3 consecutive weeks. A longer schedule was then tested as curative radiotherapy requires 5 to 6 weeks of treatment. The 3-week schedule indicated that the peripheral neuropathy might be related to an individual patient’s drug exposure. Therefore, for the first three steps of the long schedule, the drug was initially given more frequently during the first 2 to 3 weeks (i.e., four or five times per week), to allow time to “titrate” drug against the development of neuropathy toward the end of the schedule. In the second and third steps of the long schedule, this approach had the consequence of delivering as much drug during the first 3 weeks of the 5-week course as was delivered during the 3-week schedule. However, interim data analysis suggested that more dose could be administered over a longer time period leading to the development of schedules that delivered dose at a more protracted rate. Two approaches were used: a smaller single dose (1.7 rather than 2.0 g/m²), and a split course schedule consisting of 2 weeks of drug treatment, 2 weeks of rest, and 2 weeks of drug treatment. Radiotherapy was given throughout the 6 weeks.

The drug was administered in 100–200 ml of fluid by rapid infusion for ≤10 min. Each patient was to undergo one full pharmacokinetic study early in the course of treatment. Starting from the beginning of the infusion (the zero time point), serum samples were obtained at the end of the infusion and at 15, 30, 45, 60, and 90 minutes, and at 2, 4, 6, 8, or 10, and 24 h postinfusion. A 24-h urine sample was simultaneously obtained. The samples were assayed as previously described (15). The pharmacokinetic parameters of a two-compartment open model were obtained from the serum concentration data using the NIH PROPHET system (19). The model accounted for the time of the drug infusion.

Total-AUC was estimated by multiplying the single-dose-AUC by the number of doses given. The assumption that AUC was constant over the course of treatment was based on data from the DMM trial in which repeated pharmacokinetic analyses were demonstrated to be constant. Because of the expense of analysis and the inconvenience to the patients, the assumption was tested and confirmed in a subset of 23 patients in this study (see “Results”).

The correlation between clinical and pharmacokinetic parameters and neurotoxicity was investigated by means of multivariate logistic regression (20). If p is the probability of developing peripheral neuropathy, then the logarithm of the odds ratio p/(1 − p) is assumed to be a linear function of the covariates, xᵢ, as follows:

\[ \log \left( \frac{p}{1 - p} \right) = \beta_0 + \sum_{i=1}^{n} \beta_i x_i \]

The β's, the parameters of the model, are determined from patient data by maximizing the logarithm of the likelihood function in the usual way. Once the β's have been determined, the model can be used to predict the probability of developing peripheral neuropathy for other patients, if the values, xᵢ, of their covariates are known.

Results
A total of 102 patients were entered on study, 37 on the short schedule, and 65 on the long schedule. Eighty patients were evaluable for the development of our neuropathy (Table 1). It is from this group of patients that the starting dose for the phase II and III trials was selected. Seventy-one patients had sufficiently complete pharmacological data available to be included in the analysis of the correlation between pharmacokinetic parameters and toxicity. Of the 71 patients, 31 completed treatment and did not develop neuropathy, 30 developed neuropathy, and 10 did not complete treatment for reasons other than the development of neuropathy: drug allergy, 3; abnormal liver function tests of unknown etiology, 1; deterioration of general medical condition, 5; refused further treatment, 1.

The dose-lowering toxicity of SR 2508 was peripheral neuropathy consisting of numbness, a tingling sensation, dysesthesia, and occasionally pain, primarily in the lower extremities. Grade I neuropathies were mild and most resolved over a period of 2 to 6 months. Grade II neuropathies interfered with routine activities, or required analgesic medications. They tended to be long standing or irreversible, with a slow decrease in severity. Table I shows the incidence of neurotoxicity for the 80 evaluable patients based on their assigned treatment. The total amount of drug tolerated increased as the duration of the treatment course lengthened, as demonstrated by the finding that 4 of 6 patients who received 29.7 g/m² over 3 weeks were toxic, compared to 0 of 6 who received 30 g/m² over 5 weeks. In the 3-week schedule no patients tolerated a dose in excess of 30 g/m², while 3 of 8 patients in the 5- to 6-week schedule did not develop neuropathy at a dose of 40.8 g/m².

A representative pharmacokinetic profile is shown in Fig. 1. Other pharmacokinetic parameters analyzed included the α and β distribution half-lives, drug clearance, volume of distribution, serum concentrations at various time points, and the percentage of drug excreted in the urine in 24 h. Comparisons were made of pharmacokinetic profiles of 23 patients who had more than one pharmacological analysis performed. One patient had analyses done on 8 separate occasions, the others had analyses done on 2 or 3 occasions. In all cases, the curves of serum concentration versus time generated on different days of treatment were superimposable. Therefore, the total-AUC for each patient was calculated by multiplying the single-dose-AUC by the number of doses administered.

Some of the pharmacokinetic parameters obtained for the 71 patients are as follows (mean values): t₁/₂, α, 17 min; t₁/₂, β, 280 min; plasma clearance, 0.106 liters/min; volume of distribution, 320 liters; and neurotoxicity was investigated by means of multivariate logistic regression (19). The radiosensitizer phase I study differs from the usual chemotherapy phase I trial in which repeated pharmacokinetic analyses were demonstrated to be constant. Because of the expense of analysis and the inconvenience to the patients, the assumption was tested and confirmed in a subset of 23 patients in this study (see “Results”).

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<th>No. of patients toxic/total (grade II)</th>
<th>No. of patients evaluable</th>
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<td>6 other day</td>
<td>5</td>
<td>8*</td>
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* One patient had a total dose of 35 g/m².

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The single daily dose chosen for the phase II and III trials is 2 g/m² for the following reason. From limited tumor biopsy data, as up to three times as much drug can be administered (17, 18). With this severe limitation it was not surprising that MISO was not particularly effective (11, 12). A recent exception is a large randomized trial in Denmark for patients with head and neck cancer (4). Given the dose-related toxicity of MISO only five or six doses of 2 g/m² could be given. Alternatively, if drug was given with many radiation treatments a very small individual dose of approximately 0.4 g/m² was administered. With this severe limitation it was not surprising that MISO was not sufficiently less toxic than MISO to proceed to clinical trials (15).

The efficacy of hypoxic cell sensitizers in clinical radiotherapy remains to be proven. Most of the trials with MISO did not show any benefit from its use (12). A recent exception is a large randomized trial in Denmark for patients with head and neck cancer (4). Given the dose-related toxicity of MISO only five or six doses of 2 g/m² could be given. Alternatively, if drug was given with many radiation treatments a very small individual dose of approximately 0.4 g/m² was administered. With this severe limitation it was not surprising that MISO was not particularly effective (11, 12).

SR 2508 is definitely better tolerated than MISO or DMM, as up to three times as much drug can be administered (17, 18, 21). Unlike its predecessors, more SR 2508 can be given as the duration of the treatment course increases (Table 1, Fig. 2). The single daily dose chosen for the phase II and III trials is 2 g/m² for the following reason. From limited tumor biopsy data, it was observed that the tumor concentration of SR 2508 peaked shortly after the end of the infusion (17, 22), and that the tumor concentration was approximately 70% that of the serum concentration. Therefore, it is estimated that the tumor concentration will be approximately 100 μg/ml. Although the precise intracellular concentration of drug is not known, it was demonstrated, in mice, that approximately 30 min were required between achieving the maximum tumor concentration and maximum radiosensitization (23). Extrapolating to the clinical studies, the radiation treatment will be given 30 min after the start of the infusion. A concentration of SR 2508 of 100 μg/ml will produce a sensitizer enhancement ratio of approximately 1.6 for the hypoxic cells in the tumor at the time of irradiation (11, 21). The sensitizer enhancement ratio can be defined in vitro.

38 liters; percentage of unchanged drug excreted in the urine in 24 h, 70%. The most commonly used single dose of drug (42 patients) was 2.0 g/m² which produced a mean peak serum concentration (end of infusion) of 239 μg/ml, and a 1-h concentration of 78 μg/ml.

Variables included in the analysis of neurotoxicity were age, sex, weight, body surface area, Karnofsky performance status, serum concentration of drug at 1 and 4 h, total dose administered, dose-time (defined as the time in days from the first to last drug administration), and the pharmacokinetic parameters of terminal half-life, clearance, and total drug exposure (total-AUC). Only four models involving a single covariate were found to be significant at $P = 0.05$: total-AUC, $P < 0.000001$; total dose administered, $P = 0.02$; and the serum concentration at 1 and 4 h, $P = 0.03$ and $P = 0.05$, respectively. Thus, the parameter of total-AUC was much more significant than any other parameter. The three weaker covariates are all related to total-AUC, so their prognostic significance may be expected to vanish in multivariate models involving this factor. In fact, only one bivariate model, that consisting of total-AUC and dose-time, provided a better fit to the data than that of total-AUC alone.

$$\log (p/1 - p) = -8.09 + 0.274 \text{total-AUC} - 0.071 \text{dose-time}$$

No better three-covariate model was found, so this bivariate model was chosen as the best representation of the data.

A scatter plot of the values of total-AUC and dose-time for the patients included in the analysis is shown in Fig. 2. Patients indicated by a closed circle developed neuropathy ($n = 30$), whereas those indicated with an open circle did not ($n = 31$). As indicated above, some patients without neuropathy had drug discontinued for drug allergy ($n = 3$), or for reasons relating to their general medical condition ($n = 7$). Also plotted are lines representing the model predictions for the 20, 50, and 80% probability levels for developing neuropathy. It can be seen that the total-AUC tolerated increases with the time over which the drug is administered. This relationship is also suggested by the data for toxicity by step shown in Table 1. However, within a given step there can be a wide variation in the drug exposure for different patients, despite the same administered total dose in g/m².
under hypoxic conditions as the dose of radiation required to produce a certain level of cell killing without sensitizer divided by the radiation dose needed to produce the same level of cell killing in the presence of sensitizer at the concentration stated. The relationship between the 2-nitroimidazole sensitizer concentration and the sensitizer enhancement ratio is a complex log-log relationship (11). Therefore, once concentrations in the range of 100–200 μg/g of tumor are achieved, large increments in drug concentration are needed to produce modest increases in enhancement ratio.

Schwade et al. (24) suggested for results with MISO that the use of the pharmacological data would be of benefit in predicting neurotoxicity. The model developed from the data from the phase I SR 2508 study will be evaluated prospectively in the phase II and III trials. If this or a similar correlation is proven to be valid in predicting the neuropathy it will be extremely valuable in the safe use of SR 2508. The grade I peripheral neuropathy is mild, will cause little discomfort, will rarely require symptomatic treatment, and will resolve quickly. On the other hand, the grade II neuropathy can be debilitating and long lasting. The patients given SR 2508 will have accurate and prompt analysis of their serum drug profiles. If the model predicts that a given patient may develop a neuropathy, a number of maneuvers can be undertaken to avoid serious side effects. As the cumulative dose approaches the point where toxicity is expected, the drug will be discontinued at the development of any sign of toxicity. Alternatively, the drug dose could be halved as the expected toxic point arrives, in order to titrate the dose of sensitizer. If a patient has a very high serum concentration of drug at 30 min resulting in a very high AUC it might be possible to reduce the size of the individual dose. Clearly, any of these maneuvers would have to be done as part of a standardized treatment protocol.

The planned starting schedule for using SR 2508 in curative radiotherapy regimens will be 2 g/m² three times weekly up to a total dose of 34 g/m². It may be possible to increase the planned total dose slightly after more data are accumulated. Phase II and III trials are soon to begin for patients with head and neck, cervix, prostate, bladder, and possibly other cancers. Other proposed studies include the use of SR 2508 as a constant infusion with brachytherapy. A fourth 2-nitroimidazole compound, RO-03-8799, is currently being tested in England (25, 26). It has a different dose-limiting toxicity and, therefore, it might be possible to use the two sensitizers in combination (22), in a manner analogous to that of combination chemotherapy.

Since the degree of sensitization depends on the total sensitizer concentration, the use of the combination of sensitizers may allow each dose to achieve a standard course of radiation to be sensitized effectively.

In conclusion, the efficacy of hypoxic cell sensitizers in clinical radiotherapy remains to be proven. We have developed a model for the prediction of neurotoxicity based on the total-AUC and dose-time, which will be verified. If this model remains valid, SR 2508 can be used clinically with very low risk.

REFERENCES

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