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Relationship between the pharmacokinetics and toxicity of mitozolomide

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Summary. The cytotoxic drug mitozolomide has been found to cause unpredictably severe thrombocytopenia during phase I and II clinical trials. In an attempt to relate dose and pharmacokinetic parameters to toxicity, we measured plasma concentrations of mitozolomide in 14 patients with a range of malignancies. There were significant correlations (Spearman rank correlation test) between drug clearance and AUC and white blood cell nadir. The pharmacokinetic and toxicity data were not normally distributed; therefore, it was not possible to construct predictive nomograms for toxicity based on linear regression analysis.

Introduction

Mitozolomide is a novel agent with mechanistic similarities to the chloroethyl nitrosoureas [2] that has undergone phase I and limited phase II clinical trials [4, 5, 7]. In a phase II evaluation of mitozolomide in ovarian cancer, 2 of 19 patients experienced WHO grade 4 thrombocytopenia despite a dose reduction from 115 mg/m^2 (oral dose recommended by phase I trial) to 90 mg/m^2 [3]. The myelotoxicity was only partly dose-related. Therefore, the authors speculated that significant variation in the pharmacokinetic profiles between patients could have contributed to the unforeseen myelosuppression, although plasma concentrations of mitozolomide were not measured in that study.

It is well recognised that cytotoxic drugs have steep dose-response curves and, consequently, low therapeutic ratios. Based on the assumption that dose-response curves for toxicity and efficacy are parallel, most antineoplastic agents in current clinical use are given at close to the maximum tolerated dose. There are few studies relating the pharmacokinetics of cytotoxic drugs to pharmacodynamic end points such as the degree of myelosuppression [8]. If one could relate dose or other exposure parameters such as AUC to nadir white cell and platelet counts, it would be possible to develop testable, predictive models that should help to optimise drug delivery. Having undertaken phase II trials of oral mitozolomide in a range of tumour types, we carried out pharmacokinetic studies in an attempt to relate dose and plasma concentration to toxicity.

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Materials and methods

Pharmacokinetic studies were carried out in 14 patients with a range of malignancies (breast cancer, 2; lung cancer, 3; melanoma, 3; ovary, 3; bladder, 1; astrocytoma, 1; pancreas, 1). The mean age was 57 years (range, 23–77 years), the sex ratio was 4:10 (M:F) and the majority of patients had undergone prior treatment of some sort (surgery, 5; radiotherapy, 4; chemotherapy, 4; no treatment, 7). Capsules of mitozolomide were provided by the Clinical Trials Unit of May and Baker (Dagenham, UK). Following oral administration of mitozolomide (90 mg/m^2), 10-ml blood samples were collected into precooled (4° C) lithium heparin tubes and centrifuged immediately (2,000 rpm for 5 min at 4° C), and the plasma was frozen immediately at −20° C. Samples were taken prior to drug administration and at intervals thereafter (0.5, 1, 1.5, 2, 2.3, 3, 4, 6 and 8 h). All samples were stored at −20° C until analysis by HPLC [7].

The plasma concentration-time data were fitted using the method of least squares by the PCNONLIN computer programme [9, 10]. The area under the plasma concentration-time curve (AUC) from zero to infinity was derived using the trapezoidal rule, with extrapolation from the last time point to infinity. The Spearman rank correlation coefficients were derived using an in-house computer programme, as the toxicity data (nadir white cell and platelet counts) and pharmacokinetic parameters were not normally distributed (chi-square test of normality).

Results

The pharmacokinetic parameters are summarised in Table 1. The plasma concentration-time profile (Fig. 1) was best described by a one-compartment model following first-order absorption from the gastrointestinal tract. The mean lag time for absorption of the oral preparation of the drug was 0.4 h (range, 0.1–1.8 h) and the elimination half-life was 1.2 h (range, 0.5–2.2 h). The mean volume distribution was 36.9 l (range, 14–65 l) and the mean AUC was 9.2 mg h/l (range, 5.7–15.8 mg h/l). Chi-square testing of distribution revealed that the pharmacokinetic and toxicity parameters were not normally distributed; the various data sets were both negatively and positively skewed, and attempts to normalise the distribution (e.g. by log transformations) were not successful; therefore, non-parametric statistical methods were used (i.e. Spearman rank correlation coefficient).

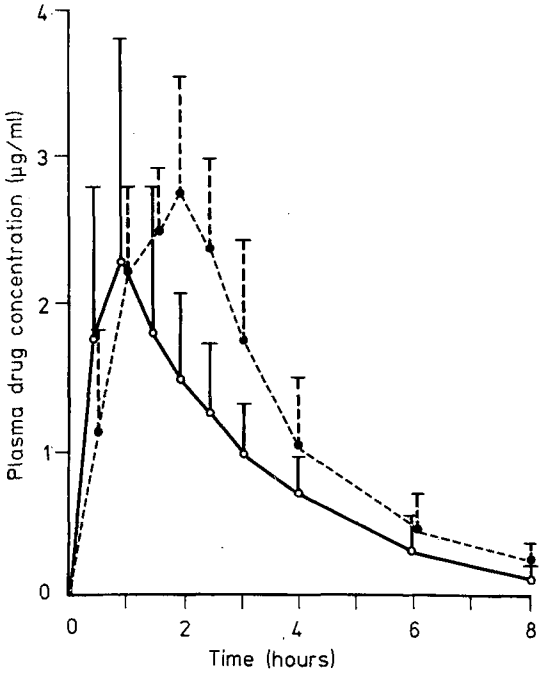

Fig. 1. Plasma concentration-time profiles following oral administration of mitozolomide. Dose range: ○, 75–89 mg/m^2 (n = 7) (mean value); ●, 90–100 mg/m^2 (n = 7) (mean value). Vertical bars denote 1 SD

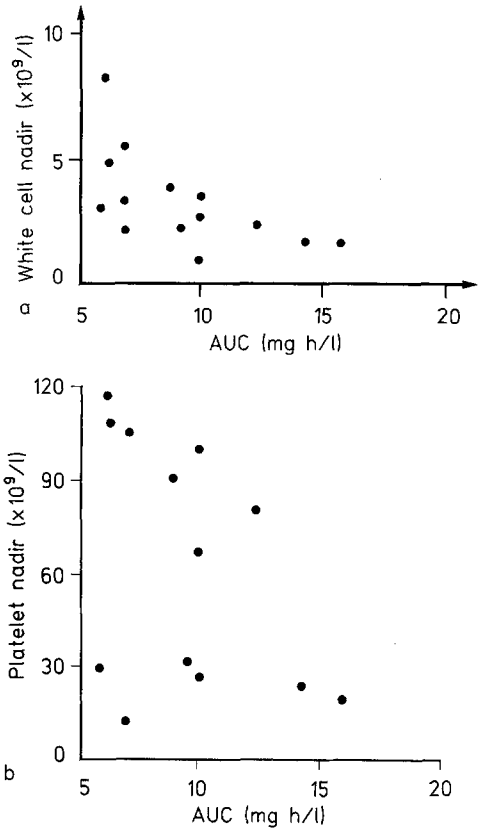

Fig. 3 a, b. Plot of nadir white cell and platelet count vs AUC for mitozolomide

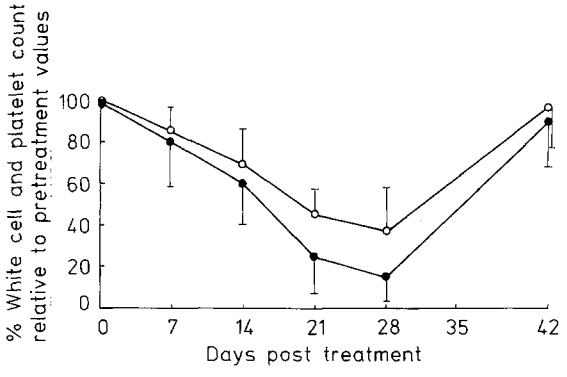

Fig. 2. Variation of white cell (○) and platelet (●) count, expressed as a percentage of pretreatment values, following oral administration of mitozolamide on day 0. The results are expressed as means and vertical bars denote 1 SD

The white cell and platelet nadir typically occurred between 20 and 30 days (Fig. 2). There was no correlation between the duration and depth of the platelet nadir. There were significant correlations between the AUC and the white cell nadir (P = 0.038; r = −0.66), drug clearance and the white cell nadir (P = 0.017; r = 0.60), the platelet nadir and the white cell nadir (P = 0.001; r = 0.77), clearance and the peak plasma concentration (P = 0.002; r = −0.64), the AUC and the peak plasma concentration (P = 0.005; r = 0.81) and the AUC and drug clearance (P = 0.0007; r = −0.83).

The white cell nadir and AUC data are presented in Fig. 3. There were no correlations between peak plasma concentration or any other pharmacokinetic parameter and the haematological indices. The AUC over arbitrary plasma concentrations (1, 2 and 3 μg/ml) were calculated; however, there were no correlations with the white cell or platelet nadirs, implying that there is not a concentration threshold effect.

Table 1. Summary of pharmacokinetic parameters and white cell/platelet nadirs

Dose (mg/m^2)	Peak plasma level (mg/l)	AUC (mg h/l)	Clearance (l/h)	White cell nadir (×10^9/l)	Platelet nadir (×10^9/l)
90±7.2 (74-100)	3.6±1.7 (1.5-6.5)	9.2±3.1 (5.7-15.8)	18.5±5.1 (10.5-25.8)	3.7±2.5 (1.0-8.2)	62±38 (12-115)

Data represent the means ±1 SD; numbers in parentheses indicate the range

Discussion

In the present study we investigated the pharmacokinetics of oral mitozolomide and found correlations between certain of its pharmacokinetic parameters and myelotoxicity. One problem that became obvious during phase II trials of mitozolomide was unpredictable thrombocytopenia [4, 5, 7]. Although the overall number of patients in the study was small, there was no clear association between myelotoxicity and dose. The authors therefore commented that detailed pharmacokinetic studies could help to explain the degree of myelosuppression experienced by some patients. There are relatively few data relating the pharmacokinetics of cytotoxic drugs to pharmacodynamic end points such as myelosuppression, although there are a few notable examples [1, 3, 6]. This approach implies definable mathematical relationships between plasma drug concentration and toxicity.

In the present study, according to the non-parametric Spearman rank correlation test, there were significant relationships between AUC or drug clearance and the white blood cell nadir. Although there was a significant correlation ($P = 0.001$) between the white cell and platelet nadirs, there were no correlations between the pharmacokinetic parameters and thrombocytopenia. The degree of leukopenia was, on the whole, mild and not clinically troublesome. However, thrombocytopenia was marked (6 of 14 patients had platelet nadirs of $<30{,}000$) and clinically more significant than leukopenia. It is possible that we could not detect a correlation between platelet count and pharmacokinetic parameters because there was greater inherent variation in the platelet nadir than in the white cell nadir. The pharmacokinetic and toxicity data were not normally distributed; therefore, it was not possible to construct predictive linear models or nomograms based on regression analysis, as has been proposed for carboplatin [1, 6].

This study emphasises the difficulties and sources of variation inherent in attempting to optimise anti-cancer drug delivery based on estimates of plasma drug concentration. It is possible that a Bayesian or population pharmacokinetic approach would help to achieve this aim, but this would depend on our ability to define a plasma therapeutic window, such as is available for digoxin, for individual antineoplastic drugs.

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