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SHORT COMMUNICATION

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Effect of filgrastim on the pharmacokinetics of MX2 hydrochloride in patients with advanced malignant disease

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Abstract *Purpose*: To investigate the effect of granulocyte colony-stimulating factor (G-CSF) on the pharmacokinetics and pharmacodynamics of the new morpholino anthracycline drug MX2. *Methods*: A total of 25 patients with advanced malignant disease participated in a dose-escalation study in the first cycle of treatment given i.v. at doses of 50–80 mg/m^2 (74–152 mg) with concomitant filgrastim (G-CSF, 5 μg/kg) given daily beginning at 24 h after the dose of MX2. *Results*: The mean fast distribution half-life (1.5 ± 1.0 min) and the mean plasma clearance (2.18 ± 0.95 l/min) were significantly lower than the respective mean values found in a previous study in which 27 patients had received MX2 (16.8–107.5 mg) alone (3.3 ± 2.2 min and 2.98 ± 1.68 l/min, respectively; $P < 0.05$). There was no correlation between plasma clearance and the delivered dose for the combined MX2-alone and MX2-filgrastim groups, indicating that the lower clearance observed in the G-CSF group was probably not due to the higher dose. Elimination half-lives of the metabolites M1 and M4 were significantly greater in the filgrastim group (19.8 ± 14.7 and 11.8 ± 5.0 h for M1 and 14.8 ± 4.1 and 12.3 ± 6.3 h for M2, respectively). Unlike the MX2-alone group, there was no relationship in the MX2-filgrastim group between the relative nadir neutrophil count and the dose or between the duration of grade IV neutropenia and the dose of MX2. *Conclusions*: This study shows that filgrastim decreased the plasma clearance of MX2 by approximately 25%, possibly by inhibition of metabolism.

Key words MX2 · Pharmacokinetics · Filgrastim G-CSF · Myelosuppression

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Introduction

KRN8602 is the hydrochloride salt of MX2 (3′-deamino-3′-morpholino-13-deoxo-10-hydroxycarminomycin), a new morpholino anthracycline that in vitro has cytotoxicity comparable with or superior to that of doxorubicin (Adriamycin), including activity against doxorubicin-resistant cell lines [8, 9]. In a recent phase I dose-escalation study the maximum tolerated dose of MX2 in patients with advanced malignancy was 40 mg/m^2 [5]. Further dose escalation was limited by neutropenia; therefore, the present study examined in a similar patient group further dose escalation, beyond 40 mg/m^2, supported by filgrastim granulocyte colony-stimulating factor. In this study it was of interest to examine the effect of filgrastim on the pharmacokinetics of MX2 as other cytokines are known to decrease the hepatic content and activity of drug-metabolising enzymes [1, 4, 6].

Table 1 Effect of filgrastim on the pharmacokinetics of MX2

	$t_{1/2\alpha}$ (min)	$t_{1/2\beta}$ (h)	$t_{1/2\gamma}$ (h)	V_c (l)	V_{ss} (l)	CL (l/min)
Filgrastim	$1.5 \pm 1.0^{*}$	1.17 ± 0.89	13.7 ± 10.6	71.8 ± 83.3	1275 ± 604	$2.18 \pm 0.95^{**}$
Alone[a]	3.6 ± 2.2	1.31 ± 1.28	10.8 ± 5.1	95.7 ± 87.3	1458 ± 749	2.98 ± 1.68

$^{*}P = 0.03$; $^{**}P = 0.04$;
[a] Data from Morgan et al. [5]

Patients and methods

A total of 25 patients participated in this study. Patients had histologically proven locally advanced or metastatic cancer along with a life expectancy of at least 2 months, an ECOG performance status of 2 or better and a neutrophil count of greater than 1.5×10^9/l. Other details of patients were similar to those described in the previous report [5].

This was an open-label phase I dose-escalation study. The pharmacokinetics of MX2 were determined once in each patient during the first cycle of treatment. The starting dose was 50 mg/m^2 and doses were increased in increments of 10 mg/m^2 to 80 mg/m^2. On the 1st day of the first cycle of treatment, patients received an i.v. dose of MX2 over 1 min. Blood samples were collected periodically over the next 48 h for MX2 analysis and over the next 19 days for full blood examination. Patients also received daily s.c. injections of filgrastim (Neupogen, Amgen) at 5 μg/kg starting on the 2nd day of the first cycle of treatment and continuing until neutrophil recovery, defined as a neutrophil count of greater than 2.0×10^9/l on two successive measurements or greater than 10.0×10^9/l on one measurement beyond the nadir.

The plasma concentrations of MX2 and its four metabolites [5] were assayed by a previously published high-performance liquid chromatography method [5, 7]. The area under the plasma concentration versus time curve to infinite time (AUC), the volume of the central compartment, the volume of distribution at steady state (V_{ss}) and the total systemic plasma clearance (CL) were calculated by standard noncompartmental methods [2]. The elimination half-life of each of the four metabolites of MX2 was determined by linear regression of the terminal log-linear portion of the plasma metabolite concentration versus time curve. The AUC value for each metabolite was determined by the trapezoidal rule with extrapolation to infinity.

The relationship between the duration of neutropenia and the drug dose (D) was examined using the Hill equation [3]:

$$E = \frac{E_{max} \cdot D^n}{(ED_{50})^n + D^n}, \quad (1)$$

where E is the drug effect (duration of neutropenia), E_{max} is the maximal drug effect, ED_{50} is the dose that causes half of the maximal effect and n is a parameter describing the slope of the relationship. The relationship between the dose, AUC or C_{max} and the nadir neutrophil count was examined using the fractional E_{max} model [3]:

$$\frac{E}{E_0} = \left[1 - \frac{C}{(IC_{50} + C)}\right], \quad (2)$$

where E is the nadir neutrophil count, E_0 is the baseline neutrophil count, C is the dose, AUC or C_{max} of MX2 and IC_{50} is the dose, AUC or C_{max} that causes a half-maximal reduction in neutrophil count.

Results

The pharmacokinetic parameters of MX2 are summarised in Table 1 and the pharmacokinetics of the metabolites are summarised in Table 2. There was no correlation between AUC and dose ($r^2 = 0.15$, $P > 0.05$), between AUC and dose per kilogram ($r^2 = 0.05$, $P > 0.05$) or between AUC and dose per square meter ($r^2 = 0.22$, $P > 0.05$).

A comparison of the pharmacokinetic data obtained in the present study, in which MX2 was given with filgrastim, was made with the data from our earlier study in which MX2 was given without filgrastim (Tables 1, 2) [5]. In the MX2-filgrastim group, the mean fast distribution half-life and the mean CL were significantly lower than those found in the MX2-alone group. As the dose of MX2 given to the MX2-alone group was lower than that delivered to the MX2-filgrastim group the relationship between CL and dose was examined for the whole patient group, and this is shown in Fig. 1. Figure 1 shows that there was no correlation between the CL and the dose of MX2, which suggests that the lower CL of MX2 observed in the filgrastim group was not due to the higher dose.

The effect of filgrastim on the elimination half-life of each of the metabolites of MX2 is shown in Table 2. This shows that the elimination half-lives of M1 and M4 were significantly greater in the MX2-filgrastim group than in the MX2-alone group (Mann-Whitney rank-sum test, $P < 0.05$). Filgrastim had no significant effect on the $AUC_{metabolite}/AUC_{MX2}$ ratio recorded for any of the metabolites (Mann-Whitney rank-sum test, $P > 0.05$).

There was no correlation between the relative nadir neutrophil count and the AUC ($r^2 = 0.002$, $P > 0.05$), C_{max} ($r^2 = 0.15$, $P > 0.05$) or total dose delivered ($r^2 = 0.0007$, $P > 0.05$), and the fit of the fractional E_{max} model to each of these relationships was also very poor. There was a shift to the right in the relationship between the relative nadir neutrophil count and the dose as recorded for the MX2-filgrastim group as compared with the MX2-alone group, reflecting the protective effect of filgrastim on the neutropenic effect of MX2

Table 2 Effect of filgrastim on the elimination of MX2 metabolites

	$t_{1/2}$M1 (h)	$t_{1/2}$M2 (h)	$t_{1/2}$M3 (h)	$t_{1/2}$M4 (h)
Filgrastim	$19.8 \pm 14.7^{*}$	20.8 ± 20.8	18.6 ± 8.6	$14.8 \pm 4.1^{**}$
Alone[a]	11.8 ± 5.0	21.9 ± 11.8	19.0 ± 11.3	12.3 ± 6.3

$^{*}P = 0.010$; $^{**}P = 0.012$;
[a] Data from Morgan et al. [5]

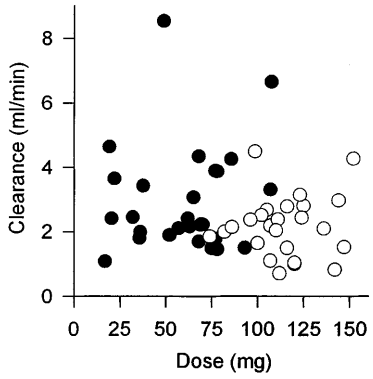

Fig. 1 Relationship between the CL and the dose of MX2 as recorded for the MX2-filgrastim group (○) and the MX2-alone group (●) (from Morgan et al. [5])

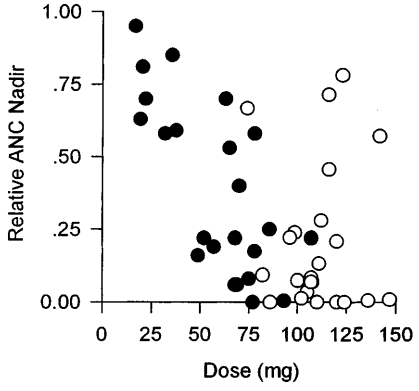

Fig. 2 Relationship between the relative nadir neutrophil count and the dose of MX2 as recorded for the MX2-filgrastim group (○) and the MX2-alone group (●) (from Morgan et al. [5])

(Fig. 2). There was also no relationship between the duration of grade IV neutropenia (i.e. the period during which the neutrophil count was less than 0.5×10^9/l) and the dose or AUC.

Discussion

The overall pattern of distribution and elimination of MX2 was broadly similar in the MX2-alone and MX2-filgrastim groups. As had been observed in the MX2-alone group, there was no correlation between CL and total body weight, lean body mass or body surface area in the MX2-filgrastim group. However, whereas there was a good correlation between AUC and dose in the MX2-alone group, there was no such correlation in the MX2-filgrastim group.

In the MX2-filgrastim group the fast distribution half-life and CL were significantly lower than in the MX2-alone group (Table 1). Although the effect of filgrastim on the fast distribution half-life is probably of no clinical significance, the significance of the lower CL value is difficult to determine. The lower CL value observed in the MX2-filgrastim group could have been due to saturation of elimination as the dose of MX2 was 50–80 mg/m^2 as compared with 10–50 mg/m^2 in the MX2-alone group. However, the lack of a correlation between the CL and the dose of MX2 for the entire 52 patients (Fig. 1) suggests that saturation of metabolism was not responsible for the decrease in CL. It was not possible to study the effect of filgrastim in a within-patient crossover study because of the unacceptable toxicity of high doses of MX2 alone. The elimination half-lives of the metabolites M1 and M4 were significantly greater in the MX2-filgrastim group than in the MX2-alone group (Table 2). This suggests that filgrastim may have also impaired the further metabolism of these two metabolites, although the metabolic fate of these metabolites is not known. It is well known that inflammatory cytokines such as interleukin-1β, interleukin-6 and tumour necrosis factor-α decrease the hepatic content and activity of the cytochrome P450 drug-metabolising enzymes and decrease the hepatic clearance of drugs such as antipyrine, hexobarbital and theophylline [1, 6]. It should be noted that filgrastim administration was commenced at 24 h after the dose of MX2 in the first cycle; therefore, the findings may underestimate the postulated effect of filgrastim on subsequent doses of MX2.

In the present study, in the MX2-filgrastim group there was no correlation between the nadir neutrophil count and the dose (Fig. 2) or between the onset of grade IV neutropenia and the dose, in contrast to the MX2-alone group [5]. This reflects the action of G-CSF, which changes the relationship between neutropenia and the dose of MX2. The absence of a relationship between neutropenia and any of the pharmacokinetic parameters of MX2 suggests that pharmacokinetic principles will not be useful in guiding the dosage for optimal haematological toxicity of MX2 in the presence of filgrastim.

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