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Altered Pharmacokinetics and Clinical Consequences of Low Dose Methotrexate plus Cisplatin in the Treatment of Advanced Head and Neck Cancer

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Abstract—*Thirty-two patients with head and neck carcinoma received a multidrug chemotherapy protocol including low dose methotrexate (LDMTX) (30 mg/m^2) and cisplatin as their initial treatment. A sensitive immunoenzymatic technique was used for systematic MTX blood monitoring (0–56 hr) in all patients. The MTX-related side effects observed in 15 patients (47%) were significantly associated with an increase in systemic drug exposure occurring early during drug infusion. The average end-of-infusion concentration varied from 8 × 10^{-7} M for nontoxic patients to 1.45 and 3.12 10^{-6} M for moderately and severely toxic patients respectively. The area under the curve (AUC) (0–56 hr) was also directly related to the increase in side-effects. Total body clearance was reduced in an inverse manner. Volumes of distribution and terminal elimination half-lives were not related to the presence or intensity of MTX side-effects. Based on these data, the institution of folinic acid rescue adapted to the MTX blood concentration, a measure previously not suggested for LDMTX, completely prevented severe toxicity in a subsequent series of 26 patients without modification of the response rate.*

INTRODUCTION

EXTENSIVE studies have been conducted on the use of low dose methotrexate chemotherapy for advanced head and neck squamous cell cancer [1]. The advantages of this now standard therapy over high dose regimens include better tolerance without any significant loss in the response rate [2]. However, in an initial study on head and neck cancer patients given an intra-arterial multidrug regimen including low dose methotrexate (LDMTX), we observed a relatively high and unanticipated incidence of severe toxic manifestations attributable to MTX (leukopenia, thrombocytopenia, mucositis). These findings have been corroborated by other investigators who have reported such uncommon MTX intolerance in head and neck cancer patients administered LDMTX iv [3] or im [4] in association with other drugs. Only two instances of toxicity related to delayed MTX elimination were mentioned in these reports [4]. These pharmacokinetic abnormalities were attributed to the coadministration of cisplatin, which was thought to alter renal MTX clearance.

In order to determine whether our initial observations were linked to altered MTX pharmacokinetics, the incidence of MTX attributable toxicities was analyzed in a pharmaco-clinical study of 32 patients. A sensitive immunoenzymatic technique [5] was used to monitor the blood MTX concentrations for all patients.

MATERIALS AND METHODS

Thirty-two patients with squamous cell carcinoma of the head and neck region (29 men, 3 women; mean age 56 yr, range 47–68) received a multidrug first intention intra-arterial protocol consisting of vincristine 0.6 mg/m^2 days 1, 7 and 13; bleomycin 10 mg/m^2 days 1, 2, 3, 4, 7, 8, 9, 10, 13, 14, 15, 16; methotrexate 30 mg/m^2 days 5, 11, 17. Methotrexate was given in a 500 ml solution of 5% dextrose in water infused over 8 hr. Cisplatin (60 mg/m^2, days 6, 18) was administered by a peripheral venous route with hyperhydration instead of by the intra-arterial route used for all other drugs.

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Toxicity evaluation

The W.H.O. classification was used for toxicity assessment:

Digestive toxicity:
- grade 2 erythema, ulcerations;
- grade 3 ulcerations, only liquid aliments possible;
- grade 4 no enteral nutrition possible at all.

Hematological toxicity:
- grade 0 white blood cells (WBC) $[10^9/l] > 4.0$ platelets (Pt) $[10^9/1] > 100$
- grade 1 WBC 3.0 – 3.9; Pt 75–100
- grade 2 WBC 2.0 – 2.9; Pt 50–74
- grade 3 WBC 1.0 – 1.9; Pt 25–49
- grade 4 WBC < 1.0 Pt < 2.5.

Patients were classified in one of three groups as a function of their toxic manifestations:

Group G1 ($n = 17$) no toxicity.

Group G2 ($n = 8$): moderate (grade 1–2) toxicity, hematological and/or digestive.

Group G3 ($n = 7$): high (grade 3–4) toxicity, hematological and/or digestive.

Evaluation of response

Response was evaluated under general anaesthesia by the surgeon before and after treatment, using the following criteria:

complete response (CR): complete disappearance of all visible or palpable tumor;

partial response (PR): regression of over 50% of the product of the two largest perpendicular diameters;

no response (NR): regression of less than 50% of the product of the two largest diameters, stabilization, or progressive disease.

Laboratory analyses

Blood methotrexate levels were measured during the last LDMTX administration (day 17 of the complete cycle). The times of sample obtention were: t_0 (just prior to the 8 hr infusion), $t_{1\ hr}$, $t_{4\ hr}$, $t_{6\ hr}$ during the infusion; $t_{12\ hr}$, $t_{24\ hr}$ following completion of infusion. Blood samples were collected in 5 ml tubes without any anticoagulant and were rapidly transferred to the laboratory, centrifuged at 2000 rpm for 10 min and stored at −20°C until analyzed. An original and sensitive immunoenzymatic technique was used for MTX quantification, as described previously [5]. The limit of sensitivity was 2×10^{-10} M, and the assay showed a cross-reactivity of 0.9% with 7OH methotrexate, the main metabolite.

Creatinine (creat.) was measured prior to initiation of the complete chemotherapy cycle by the standard colorimetric method. Serum creatinine was also measured the day after the end of the complete cycle.

Pharmacokinetic analyses [6]

$$\text{total body clearance (Cl)} = \frac{\text{dose}}{\text{AUC}}$$

$$\text{volume of distribution} = \frac{\text{dose}}{\beta\ \text{AUC}}$$

$$\text{where: } \beta = \frac{0.693}{t_{1/2}\ 24\text{–}48\ \text{hr}}$$

and $t_{1/2}$ 24–48 hr determined graphically for samples obtained 24 and 48 hr after the end of MTX infusion.

The area under the plasma concentration vs. time (0–56 hr) curve (AUC) was determined by the trapezoidal rule. AUC (56 hr − α) = $^{C}56\ \text{hr}/\beta$ represented 0.4 to 0.5% of AUC (0–56 hr), and was therefore neglected.

RESULTS

Toxic manifestations attributable to MTX were observed in 15 of the 32 patients (47%): eight had moderate side-effects (group G2) while seven had severe intolerance (group G3). Hematological toxicity predominated in group G2 (five cases). In group G3 there were two cases of digestive toxicity, two cases of hematological toxicity and three cases of both digestive and hematological toxicity.

Figure 1 shows the respective MTX blood profiles in non-toxic (group G1) and toxic cycles (groups G2 and G3 considered together). Overexposure to the drug was obvious in patients who exhibited toxic manifestations as opposed to those who had no side-effects.

It should be noted that differences in drug concentrations appeared shortly after the initiation of MTX infusion and were progressively amplified during the drug's biphasic decay phases. Table 1 lists the resulting pharmacokinetic parameters. The average end-of-infusion concentrations varied from 8×10^{-7} M for G1 to 1.45 and 3.12 10^{-6} M for G2 and G3 respectively; the relationship with the intensity of intolerance was significant.

Systemic drug exposure ($AUC_{0\text{–}56\ hr}$) was also directly related to the increase in side-effects; total body clearance was reduced in inverse manner. Statistically significant differences for these two parameters were obtained for G2 + G3 vs. G1 and for G3 vs. G1 ($P < 0.05$). Volumes of distribution and terminal elimination half-lives were not related to the presence or intensity of MTX side-effects.

All pretreatment blood creatinine levels were

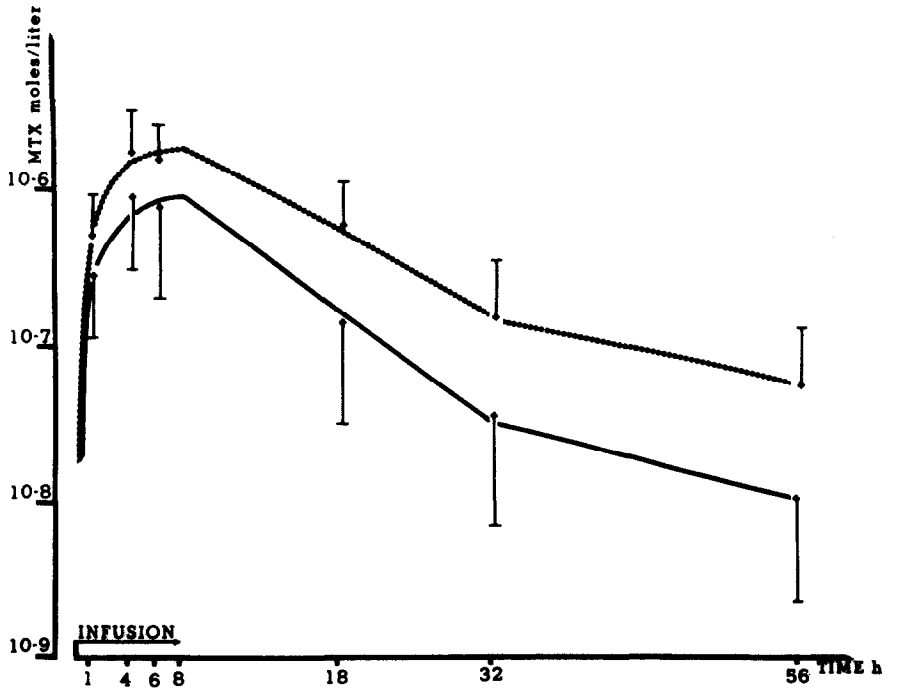

Fig. 1. Blood MTX profiles for patients with (dotted lines) and without (solid line) MTX-related side-effects

Table 1. Main pharmacokinetic parameters

	C_{inf}* 10^{-6}M	$AUC_{0-56\ hr}$ 10^2 ng hr ml^{-1}	V_d l/m^2	Cl l/hr/m^2	$t_{1/2}$ hr
Data	(15)**	(15)	(13)	(15)	(14)
Group 1: G1	08 ± 0.6	80.3 ± 46.6	142.4 ± 135.4	7.8 ± 5.9	16.1 ± 15.7
No toxicity	(0.05–2)	(16.4–163.5)	(26–500)	(2.5–25)	(5–69)
	(6)	(6)	(6)	(6)	(8)
Group 2: G2	1.45 ± 0.4	145.8 ± 78.1	68.2 ± 43.8	3.9 ± 2.3	27.6 ± 24.2
Moderate toxicity	(0.8–2)	(51.6–278.5)	(36–161)	(1.43–7.84)	(7–79)
	(6)	(6)	(6)	(6)	(6)
Group 3: G3	3.12 ± 2.3	321.25 ± 192.6	103 ± 167.4	2.9 ± 3.3	17.8 ± 8.5
Severe toxicity	(0.3–7.2)	(40–570.9)	(12.1–476)	(0.7–10)	(10–34)
	(12)	(12)	(12)	(12)	(14)
G2 + G3	2.28 ± 1.8	233.4 ± 172.6	85.6 ± 123.6	3.4 ± 2.9	23.4 ± 19.7
Toxicity in all patients	(0.3–7.2))	(40–570.9)	(12.1–476)	(0.7–10)	(7–69)
Statistics					
G1 vs. G2	$P < 0.05$	NS	NS	NS	NS
G1 vs. G3	$P < 0.05$	$P < 0.05$	NS	$P < 0.05$	NS
G1 vs. G2 + G3	$P < 0.05$	$P < 0.05$	NS	$P < 0.05$	NS
G2 vs. G3	NS	NS	NS	NS	NS

*: C_{inf} = concentration measured 6 hr after the start of infusion.
$AUC_{0-56\ hr}$ = area under the curve between the start of MTX infusion and 48 hr after the end.
V_d = volume of distribution
Cl = total body clearance
$t_{1/2}$ = half-life of the terminal phase of elimination (24–48 hr after the end of MTX infusion).
**: (number of cases)
mean ± standard deviation
(range)
Statistics by Mann–Whitney test.

within the normal laboratory range, except for one patient in G3 who had 19 mg/l (Table 2). Treatment did not significantly modify this parameter in any of the groups. However, post-treatment blood creatinine levels were significantly higher in G3 than in G1 or G2.

DISCUSSION

An unexpected, high incidence (47%) of toxic manifestations attributable to MTX was observed in this study of 32 head and neck cancer patients treated by a first intention multidrug protocol including LDMTX and cisplatin (CDDP). Differences in blood MTX levels between patients with and those without side effects were already apparent during drug infusion, and the end-of-infusion concentration was the most discriminating parameter for the occurrence and intensity of toxicity (Table 1).

This relative overexposure to the drug in patients who exhibited signs of toxicity was maintained during the biphasic decay curves (Fig. 1). Systemic drug exposure ($AUC_{0-56\ hr}$) was thus significantly and directly related to the occurrence of MTX toxicity, and an inverse relationship was observed for total body clearance (Table 1).

Despite the well-recognized association between drug intolerance and impaired elimination for high dose MTX [7,8], this report is, to our knowledge, the first to focus attention on pharmacoclinical correlations for LDMTX. MTX elimination is essentially renal [9]. Except for one patient in G3, there were no abnormal pretreatment blood creatinine levels. LDMTX toxicity could thus not be predicted on the basis of pretherapy serum creat. Coadministration of the potentially nephrotoxic drug CDDP might be thought to play a role in the induction of impaired MTX elimination, a hypothesis supported by previous reports [4] of significant LDMTX intolerance when the drug was associated with CDDP. However, treatment did not significantly modify serum creatinine levels in any of our three groups (Table 2). Only patients with severe side-effects (G3) had significantly higher post-treatment serum creatinine levels than group G1 and G2 patients. However, since MTX can induce renal failure even at moderate doses [10], it is difficult in the present case to differentiate the possible role of CDDP from that of inherent MTX toxicity. Tubular secretion is taken into account in global renal MTX elimination [11]. Thus, there is probably no strong correlation between MTX and creatinine clearances, as stressed by Kerr *et al.* [12]. Moreover, since CDDP toxicity essentially affects the proximal renal tubules [13], interference between MTX and CDDP might occur at the secretory level, without causing any concomitant alteration in serum creat. Determination of beta-2 microglobulin excretion in urine (not performed in this study) appears to be a useful indicator of renal tubule injury after CDDP administration [14]. Such a test might thus be indicated to identify patients at a high risk for MTX toxicity due to impaired renal tubule activity. Serum terminal half-lives were not significantly modified as a function of toxicity (Table 1). They were in the range of those reported by Schen and Azarnoff [9] (mean value of 27 hr). Intrinsic factors other than those governing drug elimination might thus be involved in LDMTX intolerance.

Like other authors [15–17], we [18] have established that MTX biotransformation into its less active hydrolated metabolite 7OH MTX is quantitative, and occurs shortly after the start of treatment. Although the inherent limited sensitivity of HPLC techniques [16–18] prevents measurement of 7OH MTX, defective metabolic MTX clearance might also play a role in our patients who were overexposed to the drug and showed objective signs of MTX toxicity. This hypothesis is strengthened by a recent paper reporting that patient exposure to 7OH MTX was considerable, with marked interpatient variations, in a group of advanced head and neck cancer patients treated with moderate MTX doses (100 mg/m^2) [15].

Despite the unexpected MTX side-effects, the

Table 2. Renal function and LDMTX toxicity

	Blood creatinine mg/l Normal laboratory range: 10 ± 2		
Data	Pretreatment		Postreatment
	(17)*		(17)
Group 1 : G1	9.9 ± 2.5		9.6 ± 2.2
No toxicity	(6–15)	NS**	(7–16)
	(8)		(6)
Group 2 : G2	9.4 ± 2.6		8.2 ± 1.3
Moderate toxicity	(5–14)	NS	(6–10)
	(6)		(7)
Group 3 : G3	12 ± 3.7		16.1 ± 9.3
Severe toxicity	(7–19)	NS	(9–38)
	(14)		(13)
G2 + G3	10.5 ± 3.3		12 ± 7.9
Toxicity in all pts	(5–19)	NS	(6–38)
** Intra-group statistics			
G1 vs. G2	NS		NS
G1 vs. G3	NS		$p < 0.05$
G1 vs. G2 + G3	NS		NS
G2 vs. G3	NS		$p < 0.05$

* Number of cases
Mean ± S.D.
(range)
**Intra-group statistics
Statistics by Mann–Whitney test.

multidrug protocol used gave an interesting global response rate: CR 7%, PR 65%, NR 28% (results not shown). This regimen is representative of the most effective combinations of active drugs for advanced head and neck cancers [1], and its use has been maintained. In view of pharmacological findings, however, folinic acid rescue (15 mg/m^2/6 hr) is now instituted for patients exhibiting 24-hr MTX blood levels over 5×10^{-8} M (the cytotoxic concentration limit for healthy tissue (8)); no rescue is performed below this limit. To date, 26 new patients have been treated on this basis; 11 have required folinic acid rescue due to their drug concentrations. No cases of severe toxicity have been encountered, and the response rate remains comparable. We thus advise adoption of a preventive strategy when using LDMTX, with particular care being taken for combinations including CDDP.

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Since this report was submitted, we have demonstrated that nonsteroidal anti-inflammatory drugs (NSAIDs), and particularly Ketoprofen, strongly interact with high dose MTX; the resultant dramatic delay in antimetabolite elimination can have fatal clinical consequences in certain cases (*Lancet* 1986, Feb. 1, 256–258). Patients with abnormal LDMTX elimination as in this study might be considered candidates for NSAIDs, and caution is thus urged.

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