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Letter to the editors

Removal of methotrexate by hemodiafiltration

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Dear Sir,

During the past decade, high-dose methotrexate (HDMTX) regimens have been employed in the treatment of a number of human tumors [1]. Adequate hydration, urinary alkalinization, and folinic acid (FA) rescue associated with drug monitoring are necessary to prevent severe HDMTX toxicity. Although when these are assured, HDMTX can safely be given to most patients with normal renal function, significant toxicity and occasional fatalities (up to 6% [13]) can occur unexpectedly. MTX cytotoxicity is related to both concentration and duration of exposure [8]. MTX blood cut-off levels predicting toxicity have been reported [11]. The appropriate FA dose and the duration of administration for given MTX concentrations have not been clearly defined. For these reasons, when unanticipated, potentially toxic MTX blood levels are encountered, prompt attempts to remove the drug from the circulation seem justified. An osteosarcoma patient recently treated in our institute with HDMTX was soon at unexpectedly high risk from high blood levels of MTX and underwent salvage therapy consisting in intensified FA rescue associated with successive methods of drug removal. The results obtained with each are reported in Table 1. Exchange transfusion resulted in an appreciable drop in MTX blood concentrations (from 200 to $80 \times 10^{-8} M$). Other authors have also reported that this method is effective in removing MTX from the circulation [4]. However, this approach is limited by the high blood consumption and the risk of virus transmission. Hemodiafiltration is based on the hemodialysis principle (epuration by diffusion of low molecular weight substances), but adds high convective clearance brought about by a higher rate of ultrafiltration, as in hemofiltration. Conventional hemodialysis alone is useful only for high MTX concentrations [3, 5]. Interestingly, hemodiafiltration efficiently removed MTX both at high levels (from 160 to $90 \times 10^{-8} M$) and at

Table 1. Removal of blood MTX by various methods

Date	Time	Method	MTX concentration in blood $\times 10^{-8} M$
09 Feb. 88 (MTX infusion)			
10 Feb. 88			55 000
11 Feb. 88			2 000
12 Feb. 88			460
13 Feb. 88	4 p.m.	ET	200
	5 p.m.		90
	6 p.m.		90
	7 p.m.		80
	8 p.m.		80
	10 p.m.		130
	12 p.m.		120
14 Feb. 88	Start	HDF	160
	End		90
15 Feb. 88	Start	D	65
	End		54
18 Feb. 88	Start	PE	23
	End		18
	Start	HDF	19
	End		10
19 Feb. 88	Start	PE	12
	End		12
22 Feb. 88			9
25 Feb. 88			7
29 Mar. 88			5

ET, Exchange transfusion associated with conventional dialysis (6 l blood cell concentrate and 6 l fresh plasma); HDF, hemodiafiltration (10 l replacement fluid were used for each period); D, conventional dialysis (5 h); PE, plasmatic exchange, (3.5 l exchanged each time)

Filters used: For D and HDF, BIOSPAL 2400 S AM 69 S (Hospal, Lyons, France) s = 1 m^2; for PE, CURESIS (Organon Technica, Turhout, Belgium)

Patient history: The patient (male, 47 y) presented with a voluminous malignant osteosarcoma of the mandible. Renal function was normal (creatinine = 71 μM). After a first cycle of HDMTX (12 g/m^2, 4-h infusion) without toxicity and with normal drug pharmacokinetics, he received a second cycle 3 weeks later. An abnormal pharmacokinetic profile led to a salvage protocol including intensified folinic acid rescue (100 mg/6 h, 24 h after MTX, and lasting 10 days), with successive periods of artificial drug removal. Toxicity was low, with only transient elevation of blood creatinine up to 274 μM (day 4), a thrombocytopenia with a nadir at 67 G/l (day 8), and neutropenia, but no mucositis. This acceptable toxicity is in marked contrast to the severe and even fatal manisfestations observed in patients with similar abnormal MTX levels [9]. Second-line treatment, including doxorubicin, vindesine, ifosfamide, and cisplatin, was not effective. The patient died of progressive disease 4 months later

relatively low levels (from 19 to 10×10^{-8} *M*), as shown in this case report. The results obtained with this removal method for MTX are now reported for the first time to our knowledge. In the present case, dialysis and plasmatic exchange were not satisfactory for MTX extraction. This is consistent with similar conclusions reported in previous studies by others [7] and by ourselves [12]. MTX removal by filtration-adsorption on charcoal, alone [2, 3, 5, 6] or combined in series with hemodialysis [9], seems to be an interesting alternative, but is apparently limited by a non-negligible reduction in circulating platelets [9] and by system saturability during blood passage [5, 6]. After hemoperfusion on charcoal [6, 9], exchange transfusion [4] and hemodiafiltration (see Table 1, after the second sequence), more or less marked rebounds in MTX blood concentrations occur. This pharmacokinetic phenomenon is a limiting factor in these different methods and may be attributable to release of MTX from storage tissues and/or erythrocytes [10]. For this reason, longer removal periods appear necessary for drug rebounds to be suppressed and safe levels of MTX to be achieved in blood. Hemodiafiltration would be a particularly good way of reaching this goal.

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