Eur J Cancer, Vol. 27, No. 8, p. 1060, 1991.
Printed in Great Britain
0277-5379/91 $3.00 + 0.00


# Letters

## Can Primary Osteosarcoma Act as a Third Space after High-dose Methotrexate?

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THE PHARMACOLOGY of methotrexate is well understood and at least two pharmacokinetic factors—drug concentration and duration of cellular exposure to the drug—are critical determinants of cytotoxicity. In acute lymphocytic leukaemia, the plasma pharmacokinetics of methotrexate are an independent predictor of relapse [1]. Normally the drug is cleared from plasma in two phases; the initial phase has a half-life of 2–3 h and lasts 12–24 h; the terminal phase has a longer half-life of 8–10 h [2]. This terminal half-life may be considerably prolonged in patients with renal dysfunction or third-space collections of fluid, usually a pleural effusion or ascites, and significant toxicity may result unless extended folinic acid rescue is given. We describe a case of osteosarcoma in whom the terminal half-life of methotrexate in plasma was 66 h, despite normal renal function. Although the patient had no apparent third space, we hypothesise that the primary tumour itself might have acted as such a reservoir of drug.

A 23-year-old man with osteosarcoma of the right proximal tibia was treated with combination chemotherapy before above-knee amputation. Investigations before treatment showed no evidence of metastatic disease, and in particular he had neither a pleural effusion nor ascites. His creatinine clearance and liver function tests were normal, and his only concurrent medication was paracetamol 1 g four times a day. The preoperative chemotherapy was methotrexate 8 g/m$^2$ and vincristine 2 mg, given on weeks 1, 2, 6 and 7; and doxorubicin 25 mg/m$^2$, days 1–3, on week 3. The methotrexate concentration–time profiles are plotted in Fig. 1. Each course of methotrexate 8 gm/m$^2$ was preceded by prehydration and urinary alkalinisation; methotrexate was infused over 6 h; and a forced alkaline diuresis (4 l/day) was maintained for at least 48 h. The first course of methotrexate was well tolerated, but the second was followed by WHO grade 3 mucositis despite folinic acid rescue (30 mg every 6 h for 6 days). Renal function remained normal and the third course of methotrexate caused no untoward toxicity when 45 mg folinic

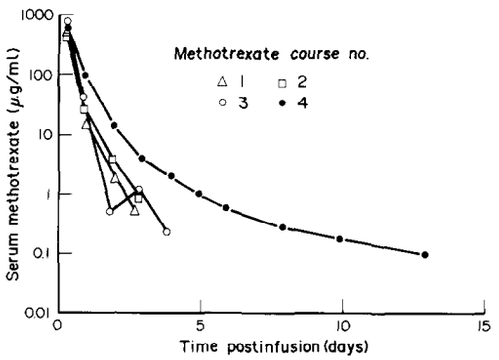


**Fig. 1. Methotrexate levels in serum.**

acid was given every 3 h. After the fourth course, methotrexate was detectable in the patient's serum 12 days post-treatment, despite 96 h intravenous fluids. Toxicity was avoided by prolonged folinic acid rescue. 15 days after the fourth methotrexate infusion, the patient underwent above-knee amputation. Histopathological examination of the tibia revealed extensive necrosis of the osteosarcoma, and less than 10% of the residual tumour cells appeared viable. Postoperatively the patient was treated with adjuvant cisplatin and doxorubicin for 3 months. Currently he remains well, with no evidence of metastases, 30 months postamputation.

The prolonged terminal half-life of methotrexate in this patient cannot be explained either by renal dysfunction or by the presence of a fluid third space. It is possible that the necrotic sarcoma has acted like a third space and has decreased the systemic clearance of methotrexate through a tissue binding effect. It was not felt to be ethically appropriate to give this patient methotrexate after removal of his tumour, although this would have clearly shown if our hypothesis was true. The case demonstrates the importance of pharmacokinetic monitoring after high-dose methotrexate and of adequate folinic acid rescue. Although it is tempting to suggest that the dramatic tumour response to chemotherapy related to prolonged exposure to methotrexate, the use of methotrexate in patients who demonstrate such delayed drug clearance, for whatever reason, is certainly hazardous, and should generally be avoided.

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Received 12 Apr. 1991; accepted 25 Apr. 1991.

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