Cancer Chemother Pharmacol (1996) 38: 566–570

SHORT COMMUNICATION

Alison H. Thomson · Margaret Daly · Janusz Knepil
Paul Harden · Paul Symonds

Methotrexate removal during haemodialysis in a patient with advanced laryngeal carcinoma

Received: 26 November 1995 / Accepted: 20 March 1996

Abstract A 62-year-old patient on long-term haemodialysis who developed an inoperable T_2N_3Mo squamous-cell carcinoma of the larynx was treated with weekly low-dose methotrexate (MTX) after failing to respond to radiotherapy. The patient was initially given one dose of 10 mg MTX (6 mg/m^2) as a 1-h infusion, then he received three further i.v. doses of 20 mg (12 mg/m^2). Haemodialysis was performed 15–18 h after each dose and the patient received folinic acid (30 mg i.v. q 6 h) until the MTX concentration was <0.1 μmol/l. The MTX concentration was measured regularly until it reached <0.1 μmol/l, and additional samples were withdrawn pre- and post-dialysis. The MTX elimination rate constant and half-life were estimated with the patient on and off dialysis. The patient failed to respond to treatment but did not experience MTX-related toxicity. The elimination half-life ranged from 22 to 42 h when he was off dialysis but fell to a median of 5.5 h during dialysis. Low-dose MTX was given to a patient on regular haemodialysis without evidence of toxicity. The rate of MTX elimination was increased during haemodialysis, although high MTX concentrations persisted for several days and prolonged rescue with folinic acid was required.

Key words **Methotrexate** · Haemodialysis · Laryngeal carcinoma · Pharmacokinetics

A. H. Thomson (✉)
University Department of Medicine & Therapeutics, West Glasgow Hospitals University NHS Trust, Glasgow G11 6NT, UK
FAX 0141 339 2800

M. Daly · P. Symonds
Beatson Oncology Centre, West Glasgow Hospitals University NHS Trust, Glasgow G11 6NT, UK

J. Knepil
Department of Pathological Biochemistry, West Glasgow Hospitals University NHS Trust, Glasgow G11 6NT, UK

P. Harden
Renal Unit, West Glasgow Hospitals University NHS Trust, Glasgow G11 6NT, UK

Introduction

Methotrexate (MTX) is well established as a useful drug in the palliative management of squamous-cell carcinoma of the head and neck. A dose of 50 mg/m^2 is effective and achieves response rates of 30–40%. Because MTX is eliminated predominantly by the kidney, its use is relatively contraindicated in patients with significant renal impairment. Consequently, there are few data describing the use of this drug in patients with chronic renal failure.

We report the case of a patient on long-term haemodialysis who developed an aggressive squamous carcinoma of the larynx, T_2N_3Mo, which failed to respond to radical radiotherapy. Low-dose MTX was then given weekly to try to prevent fungation of a large neck-node mass. MTX toxicity was avoided by frequent monitoring of levels and prolonged administration of folinic acid. We present pharmacokinetic data that show that MTX is dialysable at low concentrations.

Patient and methods

Case history

The patient was a 62-year-old retired engineer. He had a 9-cm fixed lymph-node mass in the right side of his neck that had grown rapidly over 2 months, and direct laryngoscopy revealed a T2 carcinoma of the right vocal cord involving the arytenoid. This was biopsied and showed moderately differentiated squamous carcinoma. As the node mass was fixed, the patient was unfit for surgery.

At the age of 22 years he had had a nephrectomy for renal tuberculosis. He became diabetic at the age of 56 years and was managed by diet, but at 1 year before this presentation he had developed progressive renal failure with heavy proteinuria secondary to his diabetes, and intermittent haemodialysis was commenced.

He was initially prescribed radical radiotherapy and received a total dose of 70 Gy in 35 fractions over 7 weeks to the primary tumour and neck nodes, using 5-MeV photons and a 2-phase technique. The primary tumour and both sides of the neck were initially treated with an antero-posterior parallel pair of fields to a dose of 40 Gy. Subsequently, a further 30 Gy was given using oblique fields to encompass

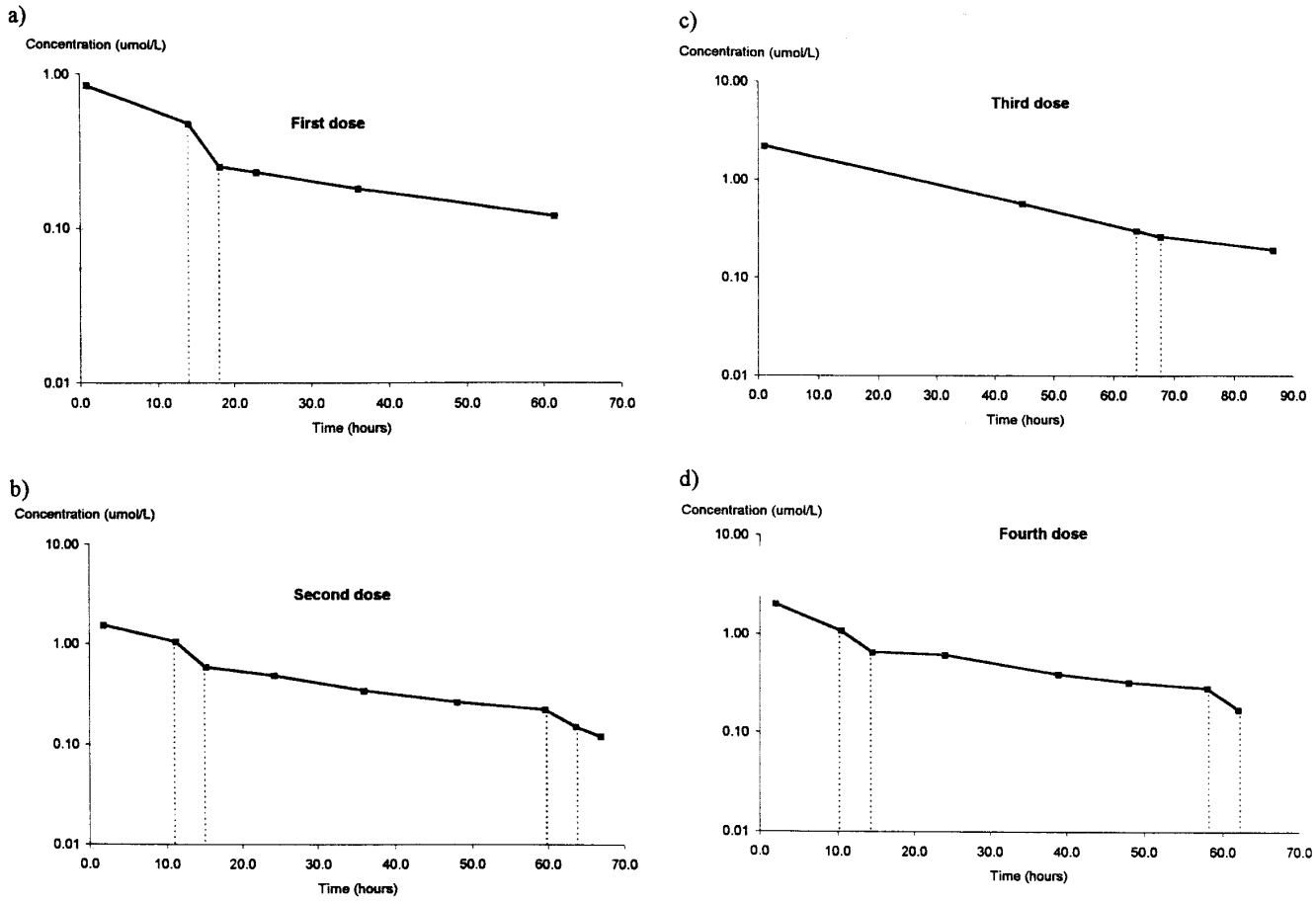

Fig. 1a–d Concentration-time profiles obtained during each course of MTX. Periods of haemodialysis are indicated by the *dotted lines*. The first dose was 10 mg; thereafter, 20 mg doses were used. **a** First dose. **b** Second dose. **c** Third dose. **d** Fourth dose

the very bulky neck-node mass. During treatment it was noted that there had been no regression of the primary tumour or neck nodes.

After 6 weeks there had been further progression of the neck-node mass and there was a 5-cm area where fungation was imminent. Surgical management would have been difficult and inappropriate given the extent of disease. However, the patient was very anxious for further treatment and after considerable discussion the option of low-dose MTX given weekly was suggested. The patient was fully informed that the treatment would be an experimental procedure given the limited knowledge of the effectiveness of dialysis in this situation.

Protocol

At the start of chemotherapy the patient had a surface area of 1.6 m^2 and his white cell and platelet counts were normal. Treatment was commenced with 10 mg MTX (6 mg/m^2) given as a 1-h infusion in 100 ml normal saline with antiemetics, then three further weekly i.v. doses of 20 mg (12 mg/m^2) were prescribed. On each occasion the patient was dialysed 15–18 h following the chemotherapy. Dialysis was typically performed over a 4-h period using a Gambro GFE 11 dialyser with a membrane thickness of 8 μm, a surface area of 1.1 m^2 and a blood-flow rate of 220 ml/min. Dialysis was repeated using the same conditions 48 h later. Urea levels fell by about 60% during dialysis and creatinine concentrations fell from around 500 μmol/l pre-dialysis to 230–300 μmol/l post-dialysis.

Folinic acid at a dose of 30 mg was started i.v. at 24 h after the MTX infusion and a total of four doses were given over 24 h. The dose was based on the nomogram of Bleyer [1]. Oral folinic acid was then substituted and continued until the MTX concentration was <0.1 μmol/l. Blood samples were taken for MTX analysis at 12- to 24-h intervals for up to 90 h following the infusion or until the MTX concentration was <0.1 μmol/l; pre- and post-dialysis concentrations were also measured. Concentrations of MTX in serum were measured by fluorescence polarisation immunoassay using the Abbott TDx. The coefficient of variation of the method was 2–6% in the range of concentrations measured.

Estimates of the elimination rate constant (k) with the patient off dialysis were determined by log-linear regression. The elimination rate constant during dialysis was determined from the relationship $C_2 = C_1 e^{-k\Delta t}$, where C_1 and C_2 are the concentrations at the beginning and end of dialysis and Δt is the interval between concentration measurements. The elimination half-life was calculated from $ln\ 2/k$. The area under the concentration-time curve was calculated by trapezoidal rule from the first concentration to the last and was extrapolated to infinity by dividing the final concentration by the off-dialysis elimination rate.

Results

Following four cycles of MTX there was no evidence of response and there was increased ulceration and pain in the neck-node mass. Chemotherapy was therefore discontinued and palliative care support at home was arranged. The patient died 2 months later. There had been no toxicity

Table 1 Estimates of the elimination rate constant elimination half-life and AUC of MTX as determined with the patient on and off haemodialysis

Course number	Dose (mg)	k (h^{-1}) On dialysis	Half-life (h)	k (h^{-1}) Off dialysis	Half-life (h)	AUC (mg h l^{-1})
1	10	0.159	4.4	0.0170	40.8	11.3
2	20	0.148	4.7	0.0226	30.7	
2		0.096	7.2			17.2
3	20	0.036	19.4	0.0315	22.0	
3				0.0167	41.6	38.8
4	20	0.127	5.5	0.0212	32.7	
4		0.125	5.5			19.2
Median	20	0.126	5.5	0.0212	32.7	18.2

associated with the MTX therapy and it was well tolerated without nausea, emesis, mucositis or myelotoxicity.

The MTX concentration-time profiles observed after each dose are illustrated in Fig. 1 and estimates of the elimination rate constant, half-life and area under the curve are shown in Table 1. The elimination half-life ranged from 22 to 42 h with the patient off dialysis (median 32 h). During dialysis there was a decrease in the elimination half-life to around 5.5 h on courses 1, 2 and 4, but the elimination half-life on course 3 was 19.4 h.

Discussion

We believe that a trial of very-low-dose MTX was justified in this patient with a fungating tumour mass and chronic renal failure. MTX is a useful drug in the palliation of advanced head and neck cancer and is frequently used in patients who are unfit for more aggressive combination chemotherapy regimens. Woods et al. [19] have shown that a dose of 50 mg/m^2 per week gives a response rate of 31% in recurrent head and neck cancer, and although doses of 500 mg/m^2 produced higher response rates, survival was not increased and the toxicity was considerably worse. In selecting a dose of 10–20 mg in this patient, we hoped to achieve MTX levels and a clinical response similar to those obtained with 50 mg/m^2. Disappointingly, our patient failed to respond despite our achieving therapeutic levels of MTX. However, this was perhaps not surprising in view of the aggressive and bulky nature of his tumour and its radioresistance.

Nevertheless, this case demonstrates that low-dose MTX can be given to patients receiving haemodialysis without predisposing them to severe toxicity, as long as concentrations are measured regularly and appropriate folinic acid rescue is given. Additionally, it was demonstrated that haemodialysis enhanced the elimination of low-dose MTX in this patient. The endogenous elimination half-life ranged from 22 to 42 h and fell to a median of 5.5 h during dialysis. On average, the elimination rate increased by a factor of 6 during dialysis, with the exception of course 3 (Table 1). The reasons for the slower elimination observed during that particular dialysis period are not clear, but it was associated with an acute deterioration in the patient's condition that may have been due to an excessive dose of slow-release morphine sulfate. This necessitated a delay in dialysis for several hours and may have contributed to the altered efficiency of removal on that occasion.

The high endogenous elimination rate that was initially observed after dose 3 may have been due to the sampling protocol. At an average distribution half-life of 3 h [18], MTX should distribute to the tissues within 12 h of dosing. However, the initial sample was taken only 1 h after the dose. The post-dialysis elimination rate of 0.017 h^{-1} was consistent with the values observed after other doses.

As the molecular weight of MTX is 454, from a theoretical point of view it should be eliminated to some extent by haemodialysis. Similarly, the protein binding of MTX has been reported as 50% [17], which should not significantly restrict its removal. In vitro studies have confirmed the dialysability of MTX and indicated that haemodialysis might have some value in detoxification [15].

In a preliminary study, Djerassi et al. [4] investigated the value of using haemodialysis or charcoal haemoperfusion to remove MTX from patients with renal impairment who were treated with a high-dose regimen. The elimination half-lives based on the first and last concentration measurements were 2.8 h in a patient with an initial concentration of 469 μmol/l who was studied at 4 h after treatment and 4.4 h in a patient who was studied at 16 h after treatment and had an initial concentration of 19 μmol/l. However, there was evidence of a biexponential decline in concentration during dialysis, which suggests that removal becomes less efficient as dialysis time increases. The authors conclude that haemodialysis is more effective if concentrations are high, but it is more likely that distribution contributed to the apparently faster elimination observed in the first patient.

Howell et al. [9] examined the influence of haemodialysis on MTX elimination in a patient who was given doses ranging from 130 to 400 mg/m^2. No obvious change in the elimination rate was observed during dialysis and further investigation revealed a low clearance rate of 0.04–0.12 ml/min across the membrane. However, the variability in the patient's endogenous elimination may have masked any influence of dialysis, and it is likely that the dialysis membrane used in the aforementioned case was less permeable that the one used for our patient.

More recent studies have focused on the use of haemodialysis to reduce toxicity in patients who have received an overdose of MTX [3] or who have developed acute renal failure in association with high-dose MTX [7, 12, 14, 16]. In most cases, haemodialysis has been supplemented with charcoal haemoperfusion, which has been shown to enhance the efficiency of drug removal significantly [3, 7, 12, 14]. One report has described a patient with unexpectedly high MTX concentrations who was successfully treated using haemodiafiltration [13], whereas high-flux haemodialysis combined with high-dose folinic acid led to a successful outcome in another case [6].

Although the potential for a rebound increase in MTX concentrations was not specifically examined in this study,

there was no evidence that this occurred because concentrations declined log-linearly after dialysis (Fig. 1). Relling et al. [14] and Hande et al. [8] observed significant rebounds in the MTX concentration measured in patients with acute renal failure who had been treated with haemodialysis and haemoperfusion [14] or with haemodialysis alone [8]. It is likely that the rebound reflected an elimination rate that exceeded the rate of transfer from tissues to blood. In contrast, Molina et al. [12] could not detect any rebound increase in the concentration when they used haemodialysis and haemoperfusion to remove MTX from a patient who had developed acute renal failure.

Data are limited on the influence of haemodialysis on low-dose MTX. Severe toxicity was observed in a 32-year-old patient on long-term haemodialysis who was given adjuvant chemotherapy for node-positive breast carcinoma [5]. This woman received one cycle of 5-fluorouracil and cyclophosphamide at reduced doses without showing signs of toxicity, but when a further cycle was given with the addition of 15 mg MTX (10 mg/m^2), she developed severe toxicity, including pancytopenia and mucositis, within 2 days. Folinic acid had been prescribed as only a single dose 3 days after chemotherapy. By day 5 the patient had developed pyrexia, neutropenia and severe stomatitis; folinic acid was therefore restarted. Her MTX concentration on day 7 was 0.5 μmol/l and took 22 days to fall below 0.1 μmol/l. Despite clearance measurements of 38–89 ml/min during dialysis, the relatively small change observed in serum MTX concentrations over the dialysis period led the authors to conclude that it had no significant effect on MTX removal.

A number of papers describe the use of MTX in patients with renal dysfunction and psoriasis or other rheumatic disorders, and a recent paper describes the use of a single 2.5-mg oral dose of MTX in two patients with severe connective-tissue disorders [10]. One patient was on continuous ambulatory peritoneal dialysis; the other was receiving haemodialysis. Neither patient had MTX levels monitored, and they did not receive folinic acid routinely. Both patients developed severe neutropenia, and one died following a prolonged episode of pancytopenia. These experiences have led these authors to recommend that MTX be avoided in patients with renal failure. However, closer monitoring and earlier administration of folinic acid might have changed their patient's outcomes.

In contrast, Yokogi et al. [20] successfully gave 20 mg MTX i.v. to a patient receiving haemodialysis. Although they found that the elimination was slow, frequent monitoring and administration of folinic acid prevented the occurrence of significant toxicity. The concentrations observed by these authors tended to be higher than ours (approximately 0.5 μmol/l after 2 days and 0.25 μmol/l after 3 days), but haemodialysis was performed for only 3 h. They have concluded that low-dose therapy with MTX can be used in patients with renal failure if they are monitored closely and receive adequate doses of folinic acid.

Folinic acid rescue is accepted as essential in the prevention of toxicity with all but very low doses of MTX. It bypasses the metabolic block caused by MTX, it may prevent further entry of MTX into the cells and it favours the drug's efflux from the cell into the interstitial fluid. It is generally recommended that folinic acid be continued until the MTX concentration falls below 0.1 μmol/l and that the dose should be adjusted according to the MTX concentration [2]. We used the nomogram proposed by Bleyer [1] to decide the folinic acid dose, and it is possible that in this case we were overcautious since the clearance of folinic acid itself might be delayed in renal failure. However, in the absence of alternative guidelines and with the suspicion that haemodialysis might remove some of the folinic acid [14], we decided to follow our standard dosing policy.

A relationship between the area under the plasma concentration-time curve (AUC) and the occurrence of toxicity was demonstrated by Milano et al. [11] in a group of 32 patients. They found that patients without toxicity, those with mild toxicity and those with moderate toxicity had mean AUC values of 8.0, 15 and 32 mg h l^{-1}, respectively. We used doses of 10 and 20 mg (6–12 mg/m^2) on an empirical basis in the hope that the patient's exposure would be similar to that encountered with 50 mg/m^2. The estimated AUC value was approximately 11 mg h l^{-1} for the 10-mg dose and ranged from 17 to 39 mg h l^{-1} for the 20-mg dose. These findings indicate that our patient would have been at risk of developing moderately severe toxicity had folinic acid not been given.

In conclusion, MTX was given in a modified low dose (10–20 mg) to a patient with an aggressive T_2N_3Mo laryngeal carcinoma who was receiving haemodialysis for chronic renal failure. Haemodialysis increased the rate of MTX elimination, although high concentrations persisted for several days. However, the administration of folinic acid until MTX concentrations fell below 0.1 μmol/l prevented the development of significant toxicity.

Acknowledgements The authors would like to thank Dr. Brian Junor, consultant nephrologist, for helpful comments and Dr. Shinichiro Ueda, research fellow, for translating the Japanese reference.

References

1. Bleyer WA (1978) The clinical pharmacology of methotrexate. New applications of an old drug. Cancer 41: 36
2. Capizzi RL, DeConti RC, Marsh JC, Bertino JR (1970) Methotrexate therapy of head and neck cancer: improvement in therapeutic index by the use of leucovorin "rescue". Cancer Res 30: 1782
3. Dalla Vale F, Cochat P, Bouffet E, Frappaz D, Bigot P, Vial M, Glastre C, Floret D (1994) Intoxication aigue au methotrexate: interet del l'hemodialyse couplee à l'hemoperfusion sur charbon active. Ann Pediatr (Paris) 41: 60
4. Djerassi I, Ciesielka W, Kim JS (1977) Removal of methotrexate by filtration-adsorption using charcoal filters or by hemodialysis. Cancer Treat Rep 61: 751
5. Ellman MH, Hou S, Ginsberg D (1990) Low-dose methotrexate and severe neutropenia in patients undergoing renal dialysis. Arthritis Rheum 33: 1060

6. Gauthier E, Gimonet JF, Piedbois P, Rostoker G, Buisson C, Ben Maadi A, Samyn B, Messadi AA, Brun B, Feuilhade F (1990) Effectiveness of hemodialysis in a case of acute methotrexate intoxication. Presse Med 19: 2023
7. Grimes DJ, Bowles MR, Buttsworth JA, Thomson DB, Ravenscroft PJ, Nixon PF, Whiting RF, Pond SM (1990) Survival after unexpected high serum methotrexate concentrations in a patient with osteogenic sarcoma. Drug Safety 5: 447
8. Hande KR, Balow JE, Drake JC, Rosenberg SA, Chabner BA (1977) Methotrexate and hemodialysis. Ann Intern Med 87: 495
9. Howell SB, Blair HE, Uren J, Frei E (1978) Hemodialysis and enzymatic cleavage of methotrexate in man. Eur J Cancer 11: 787
10. Langleben A, Hollomby D, Hand R (1982) Case report: management of methotrexate toxicity in an anephric patient. Clin Invest Med 5: 129
11. Milano G, Thyss A, Renee N, Vallicioni J, Santini J, Schneider M, Demard F (1986) Altered pharmacokinetics and clinical consequences of low dose methotrexate plus cisplatin in the treatment of head and neck cancer. Eur J Cancer Clin Oncol 22: 843
12. Molina R, Fabian C, Cowley B (1987) Use of charcoal hemoperfusion with sequential hemodialysis to reduce serum methotrexate levels in a patient with acute renal insufficiency. Am J Med 82: 350
13. Montagne N, Milano G, Caldani C, Bracco J, Ayela P, Cassuto E, Thyss A, Schneider M (1989) Removal of methotrexate by haemodiafiltration. Cancer Chemother Pharmacol 24: 400
14. Relling MV, Stapleton FB, Ochs J, Jones DP, Meyer W, Wainer IW, Crom WR, McKay CP, Evans WE (1988) Removal of methotrexate, leucovorin and their metabolites by combined hemodialysis and hemoperfusion. Cancer 62: 884
15. Sauer H, Fuger K, Blumenstein M (1990) Modulation of cytotoxicity of cytostatic drugs by haemodialysis in vitro and in vivo. Cancer Treat Rev 17: 293
16. Thierry FX, Vernier I, Dueymes JM, Roche H, Canal P, Meeus F, Pourrat JP, Conte JJ (1989) Acute renal failure after high dose methotrexate therapy. Nephron 51: 416
17. Wan SH, Huffman DL, Azarnoff DL, Stephens R, Hoogstraten B (1974) Effect of route of administration and effusions on methotrexate pharmacokinetics. Cancer Res 34: 3487
18. Winter ME (1994) Methotrexate. In: Koda-Kimble MA, Young LY (eds) Basic clinical pharmacokinetics. Applied Therapeutics, Vancouver p 266
19. Woods RL, Fox RM, Tattersall MHN (1981) Methotrexate treatment of squamous-cell head and neck cancers: dose-response evaluation. BMJ 282: 600
20. Yokogi H, Yamasaki Y, Ishibe T (1993) M-VAC therapy in a patient with ureteral carcinoma accompanied by chronic renal failure. JPn J Cancer Chemother 20: 2405