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Renal impairment following the combined use of high-dose methotrexate and procarbazine

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Summary. A major side-effect of high-dose methotrexate is renal toxicity, wich may develop unexpectedly despite adequate standard precautions such as hydration and alkalinisation of the urine. The pathogenesis is unclear. Recent reports suggest that the combination of high-dose methotrexate with non-chemotherapeutic agents may cause such renal impairment. Three cases of unexpected renal impairment following the combined use of high-dose methotrexate and another cytotoxic agent, procarbazine, are reported. Possible mechanisms of this interaction are discussed, as are recommendations for future combined administration.

Introduction

High-dose methotrexate with leucovorin has been used in the treatment of a number of human tumours. A major side-effect is renal toxicity, wich may still occur despite the use of adequate hydration, alkalinisation and forced diuresis [6, 7]. The consequent delayed renal clearance of methotrexate can then result in high serum levels predisposing to further servere toxic side-effects, e. g. myelosuppression, gastrointestinal mucositis, acute desquamating dermatitis and even death [17]. The pathogenesis of the renal dysfunction is unclear. Recent reports indicate that the combination of high-dose methotrexate with non-chemotherapeutic agents may lead to increased renal impairment [2, 3, 9, 10]. We report on three cases of unexpected renal impairment following the combined use of two cytotoxic drugs: high-dose methotrexate and procarbazine.

Materials and methods

At the Royal Marsden Hospital, between December 1983 and December 1984 patients with medulloblastoma and certain other selected CNS tumours were treated with so-called "sandwich" chemotherapy. Vincristine, procarbazine and high-dose methotrexate were used in combination after surgery and prior to central nervous system irradiation, as shown in Table 1. Four patients were treated exactly in accordance with this protocol. Procarbazine was given on days 1–14, and the first dose of methotrexate was infused within 48 h of the termination of procarbazine.

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No patient had received previous chemotherapy. Renal function in all patients was assessed by measuring the plasma creatinine level and the SICrEDTA clearance prior to chemotherapy. All patients had normal renal function and none had a history of renal disease. Particular attention was paid to standard high-dose methotrexate administration precaution, including pre- and post-hydration, alkalinisation of urine, and adequate leucovorin rescue, dependent on plasam methotrexate levels measured at 24, 48 and 72 h after methotrexate administration. Renal function was monitored by serial measurement of plasma creatinine levels at intervals after methotrexate infusion.

Results

In three of the first four patients (see Table 2) treated with this chemotherapy, renal function deteriorated after high-dose methotrexate infusion. On the 1st or 2nd day following methotrexate, the plasma creatinine level rose, the SICrEDTA clearance fell and raised serum methotrexate levels were noted at 24, 48 and 72 h (see Fig. 1). Deterioration in renal function meant that either the second dose of methotrexate was delayed (case 1 and 3) or further chemotherapy was abandoned (case 2). Three month after the study the serum creatinine had remained within normal lim-

Table 1. "Sandwich" chemotherapy protocol for brain tumours

Chemotherapy		Days
Procarbazine	100 mg/m² p.o. daily	1 → 14
Vincristine	1.5 mg/m² i.v. weekly	1 8 15 22 29 36
Methotrexate	2 g/m² i.v. infusion over 6 h × 3	15 22 29
Radiotherapy to commence on day 36		

Table 2. Patients treated with the combined chemotherapy

Case	Sex	Age	Diagnosis
1	M	12 years	Recurrent 4th ventricle ependymoma
2	F	9 years	Medulloblastoma
3	M	28 years	Recurrent cerebellar haemangioblastoma
4	F	7 years	Medulloblastoma

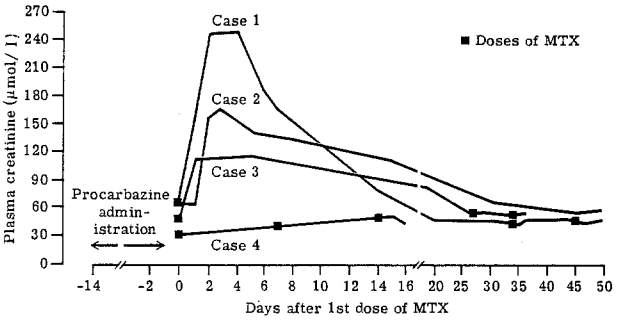

Fig. 1. Rise in plasma creatinine following methotrexate administration

its in all three cases. No other side-effects of methotrexate toxicity were recorded.

Observation in other patients with intracranial tumours following high-dose methotrexate administration

1. Three other patients with medulloblastoma not included in the present study were treated between December 1983 and December 1984 using the same chemotherapeutic programme. However, these patients received methotrexate 4, 5 and 12 days, respectively, after the administration of procarbazine was completed, the increased interval between the two drugs being the result of delays in hospital admission (2 cases) and neutropenia (1 case). None of these patients developed impaired renal function.
2. Prior to the use of the present protocol, 12 patients with medulloblastoma were treated between November 1982 and December 1983 using vincristine 1.5 mg/m^2 and methotrexate 1.5 g/m^2 with leucovorin rescue without procarbazine. None of these patients developed impaired renal function.
3. Since the appraisal of our three cases of renal failure, we have modified the chemotherapy protocol. The methotrexate infusion is now started not less than 72 h after the last dose of procarbazine. Of three patients treated according to this altered regimen none has developed renal impairment.

Conclusion

We describe three cases of renal impairment following treatment with high-dose methotrexate. This is a recognised complication of methotrexate therapy [1, 4]. However, it is clear from our observations that this renal impairment was not due to methotrexate alone, but to the combined use of high-dose methotrexate and procarbazine with an interval of less than 48 h between the two.

Discussion

No case of renal impairment has been reported following the use of procarbazine alone. The combination of procarbazine and methotrexate is being used in the management of other malignancies, such as recurrent oat cell carcinoma of the lung [8], squamous carcinoma of the lung [11] and refractory lymphoma [5]. Renal failure has not been reported as a complication of these regimens, but the dose of methotrexate used is relatively low (100–200 mg/m^2).

We have found that high-dose methotrexate (2 g/m^2) given within 48 h of administration of procarbazine caused renal impairment in three out of four cases. It is difficult to determine the site of the interaction between procarbazine and high-dose methotrexate. Procarbazine appears to increase susceptibility to methotrexate toxicity in the kidney but not to exacerbate other toxic side-effects. This effects appears not to be dose-dependent. One possible explanation would be the competitive excretion of both methotrexate and procarbazine. In our cases, however, by the time methotrexate was administered much of the procarbazine would have already been eliminated through the kidneys. A more likely explanation is that procarbazine has a transient effect on the kidneys, wich alters renal excretion of methotrexate. If high-dose methotrexate is adminstered before recovery from this change, excretion of the drug is delayed and subsequent prolonged exposure of the kidneys to methotrexate results in further impairment of renal function.

On the basis of the above observations it seems advisable to allow an interval of not less than 72 h between administration of the final dose of procarbazine given over the usual 14 days and high-dose methotrexate (2 g/m^2). If a more prolonged adminstration of procarbazine is required then a longer interval may be needed before high-dose methothrexate administration. With the wider use of high-dose methotrexate, special care should be taken to avoid possible adverse interactions with concomitant administration of other drugs.

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References

1. Abelson HT, Fosburg MT, Beardsley GP, Goorin AM, Gorka C, Link M, Link D (1983) Methotrexate-induced renal impairment; clinical studies and rescue from systemic toxicity with high-dose leucovorin and thymidine. J Clin Oncol 1: 208
2. Bleyer WA (1978) The clinical pharmacology of methotrexate: new application of an old drug. Cancer 41: 36
3. Freeman-Narrod M, Kim JS, Ohanissian H, Mills K, Smiley JW, Djerassi I (1982) The effect of high-dose methotrexate on renal tubules as indicated by urinary lysozyme concentration. Cancer 50: 2775
4. Jaffe N, Traggis D (1975) Toxicity of high-dose methotrexate (NSC-740) and citrovorum factor (NSC03590) in osteogenic sarcoma. Cancer Chemother Rep 6: 31
5. Lachant NA, Cooper MR (1981) Methotrexate, VW-26, procarbazine and dexamethasone in the treatment of refractory lyphoma. Proc Am Assoc Cancer Res 22: C-278
6. Pitman SW, Frei E III (1977) Weekly methotrexate – calcium leucovorin rescue: effects of alkalinization on nephrotoxicity; pharmokinetics in the CNS; and use in CNS non-Hodgkin's lymphoma. Cancer Treat Rep 61: 695
7. Pitmann SW, Parker LM, Tattersall MHN (1975) Clinical trial of high-dose methotrexate (NSC-740) with citrovorum factor (NSC-3590) Toxicologic and therapeutic observation. Cancer Chemother Rep 6: 43
8. Poplin EA, Aisner J, Van Echo DA, Whitacre M, Wiernik PH (1982) CCNU, vincristine, methotrexate and procarbazine treatment of relapsed small cell lung carcinoma. Cancer Treat Rep 66: 1557
9. Spector GB, Wang Y-M, Gleiser CA, Chan RC, Van Eys J (1980) Effect of gentamicin and irradiation on the toxicity of high-dose methotrexate in rats. Cancer Treat Rep 64: 989

10. Thyss A, Milano G, Kubar J, Namer M, Schneider M (1986) Clinical and pharmacokinetic evidence of a life-threatening interaction between methotrexate and ketoprofen. Lancet: 256
11. Vogelzang NJ, Bonomi PD, Rossof AH, Wolter J (1978) Cyclophosphamide, adriamycin, methotrexate and procarbazin (CAMP) treatment of non-oat cell bronchogenic carcinoma. Cancer Treat Rep 62: 1595
12. Von Hoff DD, Penta JS, Helman LJ, Slavik M (1977) Incidence of drug-related deaths secondary to high-dose methotrexate and citrovorum factor administration. Cancer Treat Rep 61: 745

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