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Methotrexate-related deaths in patients previously treated with *cis*-diamminedichloride platinum

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Summary. *Among 106 patients treated with conventional-dose methotrexate (MTX) following prior therapy with cis-diamminedichloride platinum (CDDP), six died with clinical manifestations of MTX toxicity. Death occurred 6–13 days after the administration of 20–50 mg/m² MTX. Toxicity included severe stomatitis and myelosuppression, which appeared in all six patients, skin rash in five, and diarrhea in four. Renal failure appeared in five cases and hepatic toxicity in four. All these patients had received MTX earlier without developing any serious toxicity. At the time of the last MTX administration, all had normal blood counts and also normal kidney and liver function tests. Prior therapy with CDDP may be responsible for this relatively high incidence of MTX-related deaths.*

Introduction

Methotrexate (MTX)-related death occurs in about 6% of patients receiving this agent in high doses [10]. However, mortality following conventional doses is uncommon. In this paper we report on six patients who died following conventional-dose MTX administration. It is suggested that prior therapy with *cis*-diamminedichloride platinum (CDDP) might have played a role in the fatal reactions observed in these cases.

Materials and methods

Between July 1980 and December 1982, 106 patients were treated in our center with drug combinations containing conventional-dose MTX and CDDP. The majority of these patients (59 cases) had advanced carcinoma of the head and neck region; 29 had inoperable non-small-cell bronchogenic carcinoma; and the remaining 18 had squamous cell carcinoma at other sites.

Patients with squamous cell carcinoma of the head and neck region and of sites other than the bronchus were treated with the BMP combination, which consists of bleomycin, 10 U IM on days 1, 8, and 15; MTX, 40 mg/m² IM on days 1 and 15; and CDDP, 50 mg/m² IV on day 4. Cycles were repeated every 21 days. Patients with bronchogenic carcinomas were treated by several combinations of MTX, CDDP, bleomycin, and vincristine. Plasma MTX levels were determined by the EMIT assay.

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Results

Six of the patients (i.e., 6% of the 106) died, with a typical clinical course (Tables 1 and 2). All six patients developed stomatitis 2 or 3 days after the last MTX administration. It became progressively more severe, with ulceration and bleeding that made eating and drinking impossible. This was followed by fever and leukopenia. There was a gradual deterioration, with the appearance of severe myelosuppression in all six cases, renal failure in five, hepatic dysfunction in four, and diarrhea in four. Five of the six patients developed skin rash, and in three of them it was generalized. One patient developed massive pneumonia and Klebsiella sepsis. In the remaining five patients, blood and urinary cultures were sterile. Death occurred 5–13 days after MTX despite vigorous antibiotic treatment.

Details of the treatment with MTX and CDDP and of other cytotoxic agents given concurrently with the last MTX administration are summarized in Table 3. Death occurred following the administration of 20–50 mg/m² MTX. The total cumulative dose of CDDP given previously ranged from 50 to 215 mg/m². The time interval between the last MTX administration and the last CDDP therapy ranged in five patients from 12 days to $7^1/_2$ months. In the remaining patient, the last doses of MTX and CDDP were given on the same day. Until the last administration of MTX, none of the six patients had developed any serious side-effect.

Nephrotoxicity due to CDDP developed in two cases (patients 1 and 3) and was mild and transient. At the time of the last MTX administration, the blood counts and the kidney and liver function tests of all the patients were normal. (Except for the creatinine clearances, which showed a wide range of values: 76 ml/min in patient 1; 122 ml/min in patient 2; 37 ml/min in patient 3; 50 ml/min in patient 4; 67 ml/min in patient 5; 51 ml/min in patient 6.) Two of the patients (5 and 6) were in poor general condition (Karnofsky performance status 60), and one (5) had moderate pleural effusion. The remaining four had a Karnofsky performance status of 80 or more and showed no clinical evidence of effusions. None of the six patients had been taking salicylates at that time.

Plasma MTX levels were assessed in two cases. In patient 5 this level was $8 \times 10^{-8} M$ 7 days after the last MTX administration, and in patient 6 it was $1.7 \times 10^{-7} M$ 4 days after MTX administration. They were started on leucovorin as soon as the results were known, but to no avail.

Table 1. Patient characteristics and clinical course

Patient no.	Sex/age (diagnosis)	Skin reaction (type)	Fever (highest temperature reached)	Time of death (days following last MTX)	Other side-effects
1	Male/69 (squamous cell carcinoma of the scrotum)	Generalized erythroderma with bullous eruption	39.1° C	11	Conjunctivitis, diarrhea
2	Male/51 (squamous cell carcinoma of the arm)	Generalized vesicular and erythematous	38.2° C	12	Diarrhea
3	Male/68 (squamous cell carcinoma of the tongue)	Maculopapular with ulcerations involving the scrotum, perianal region and elbows	38.3° C	13	Purpura and melena
4	Male/55 (squamous cell carcinoma of the tongue)	Generalized maculopapular	39.0° C	8	None
5	Female/58 (adenocarcinoma of bronchus)	Maculopapular involving the chest and neck	39.0° C	8	Bloody diarrhea
6	Female/74 (adenocarcinoma of bronchus)	None	38.0° C	5	Diarrhea, massive pneumonia, Klebsiella sepsis

Table 2. Laboratory findings in six patients with fatal MTX toxicity

Patient no.	Hematological toxicity			Hepatotoxicity		Renal toxicity	
	WBC nadir (per mm^3)	Platelets nadir (per mm^3)	Hemoglobin nadir (g %)	Serum bilirubin [total/direct (mg/dl)]	SGOT[a]	Urea (mg/dl)	Creatinine (mg/dl)
1	900	20,000	8.6	5.9/3.8	Normal	196	4.1
2	1,200	18,000	8.2	17.4/9.6	116	123	2.8
3	200	10,000	7.6	3.1/1.9	83	84	1.55
4	700	27,000	8.0	1.8/0.5	79	Normal	Normal
5	600	35,000	4.4	Normal	Normal	148	2.35
6	100	10,000	5.5	Normal	Normal	86	5.2

[a] Reitman-Frankel units (upper limit of normal range = 45)

Table 3. Details of MTX and CDDP therapy

Patient no.	Dose and route of last MTX administration	Total cumulative dose of MTX given prior to last MTX administration	Time interval between last MTX and prior MTX administration	Total cumulative dose of CDDP given	Time interval between last CDDP and last MTX administration	Other cytotoxic agents given concurrently with last MTX
1	50 mg/m^2 IV	440 mg/m^2	6½ months	215 mg/m^2	7½ months	5-Fluorouracil, 500 mg/m^2 IV; cyclophosphamide, 500 mg/m^2 IV
2	40 mg/m^2 IM	80 mg/m^2	14 days	50 mg/m^2	25 days	Bleomycin, 10 U IM
3	40 mg/m^2 IM	330 mg/m^2	3¾ months	125 mg/m^2	4 months	Bleomycin, 10 U IM
4	20 mg/m^2 IM	80 mg/m^2	7 days	50 mg/m^2	18 days	Bleomycin, 10 U IM
5	40 mg/m^2 IM	40 mg/m^2	15 days	60 mg/m^2	12 days	Bleomycin, 15 U IM
6	20 mg/m^2 IM	60 mg/m^2	6 days	190 mg/m^2	Both administered on the same day	Bleomycin, 20 U IV

Discussion

In a review of 498 patients treated by means of high-dose MTX and citrovorum factor rescue, Von Hoff et al. [10] found 29 (6%) drug-related deaths. As stated by Djerassi et al. [4], death is unpredictable in these cases and may occur even in 'good-risk' individuals with normal renal function, despite the usually effective dose schedule of citrovorum factor.

Mortality from low-dose MTX is uncommon in the absence of certain risk factors which are known to increase MTX toxicity. Such factors include impaired renal function, hepatic dysfunction, the presence of effusions, poor general condition [5], and concurrent administration of MTX and drugs that are organic acids, such as salicylates. The latter compete with MTX for renal transport and thus decrease its excretion rate [1, 7].

In the present series, there were six cases (6%) of fatal reactions following the administration of 20–50 mg/m^2 MTX. The clinical and laboratory course of these fatal reactions were typical of severe MTX toxicity. It is important to note that four of these six were good-risk patients and that their fatal reactions could not be ascribed to any of the known risk factors. Moreover, the severity of MTX toxicity was unpredictable, since all these patients had previously received MTX without developing any serious toxicity.

MTX is cleared mainly by the kidney, with 95% excreted within 30 h [1]. CDDP is nephrotoxic [3] and thus can interfere with MTX clearance. In a study conducted by Pitman and co-workers, the sequential use of CDDP and high-dose MTX proved to be nephrotoxic and decreased the amount of MTX that could be administered subsequently [9]. In another series [8], the combination of conventional-dose MTX, CDDP, and bleomycin had moderate to severe side-effects, and there was one case of fatal toxicity which resulted from the administration of MTX in the presence of CDDP-induced renal impairment. These authors concluded that careful attention should be paid to the potentially lethal interaction of CDDP nephrotoxicity and MTX.

Severe MTX toxicity appeared in our patients in the absence of the usual signs of renal dysfunction. And while in some of our patients the creatinine clearance was somewhat low (in the face of a normal serum creatinine), two had a normal CCT value. It should be stressed that altered tubular function, not necessarily reflected in measurements of creatinine clearance, may be responsible for a decreased excretion rate of MTX [2]. Decreased MTX clearance would result in an increased duration of exposure of normal tissues to MTX. Since the duration of exposure to MTX is considered the most important factor for MTX toxicity [1, 6,11], such patients will experience an increased toxicity. The finding, in two of the patients, of plasma MTX levels of $8 \times 10^{-8} M$ and $1.7 \times 10^{-7} M$ at 7 and 4 days, respectively, after MTX administration, is consistent with the above explanation. Perhaps serial determination of the maximum urine concentration (Umax) will prove useful in detecting very early kidney damage resulting from CDDP.

In view of our experience, special care has been taken with patients receiving MTX following CDDP. Since January 1983, plasma MTX level determination has been performed in all patients with signs of severe MTX toxicity. One patient developed severe stomatitis, generalized skin rash, diarrhea, fever, renal dysfunction, and severe myelosuppression (WBC 100/mm^3, platelets 25,000/mm^3, Hb 5.2 g%) following 40 mg/m^2 MTX. The plasma level of MTX was $4.5 \times 10^{-7} M$ 6 days after its administration. Therefore, leucovorin 10 mg/m^2 was given every 6 h for eight doses until the plasma MTX level declined to $1 \times 10^{-7} M$. This patient recovered completely.

In conclusion, we believe that care should be exercised in the case of patients receiving MTX following CDDP administration. The plasma MTX level should be determined in any patient developing prominent signs of MTX toxicity, and leucovorin rescue should be considered.

References

1. Bleyer WA (1978) The clinical pharmacology of methotrexate. Cancer 41: 36–51
2. Chabner BA, Donehower RC, Schilsky RL (1981) Clinical pharmacology of methotrexate. Cancer Treat Rep [Suppl 1] 65: 51–54
3. Dentino M, Luft FC, Yum MN, Williams SD, Einhorn CH (1978) Long-term effects of *cis*-diamminedichloride platinum (CDDP) on renal function and structure in man. Cancer 41: 1274–1281
4. Djerassi I, Kim JS, Nayak N, Dhanissian H, Adler S, Hsieh S (1977) New "rescue" with massive doses of citrovorum factor for potentially lethal methotrexate toxicity. Cancer Treat Rep 61: 749–750
5. Greenspan EM (1975) Clinical cancer chemotherapy. Raven Press, New York, p 49
6. Keefe DA, Capizzi RL, Rudnick SA (1982) Methotrexate cytotoxicity for L5178Y/Asn lymphoblasts: relationship of dose and duration of exposure to tumor cell viability. Cancer Res 42: 1641–1645
7. Mandel MA (1976) The synergistic effect of salicylates on methotrexate toxicity. Plast Reconstr Surg 57: 733–737
8. Murphy WK, Valdivieso M, Bodey GP et al (1980) *cis*-dichlorodiammine platinum-II (DDP), methotrexate (MTX) and bleomycin (BLM) chemotherapy for patients with advanced squamous cell carcinoma of the head and neck. Proc AACR/ASCO 21: 166
9. Pitman SW, Mino DR, Papac R et al. (1979) Sequential methotrexate-leucovorin (MTX-LCV) and *cis*-platinum (CDDP) in head and neck cancer. Proc AACR/ASCO 20: 419
10. 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: 745–748
11. Zaharko DS (1974) Pharmacokinetics and drug effect. Biochem Pharmacol [Suppl 2] 23: 1–8

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