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Letter

Methotrexate-induced pancytopenia and death in the Japanese literature

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Key words Methotrexate (MTX) · Pancytopenia · Rheumatoid arthritis (RA) · Side effect

To the Editor:

Methotrexate (MTX) has been used as one of the disease-modifying antirheumatic drugs (DMARD) in Japan since March 1999 under the brand name of Rheumatrex at 6 mg/week with a maximum dose at 8 mg/week. Because MTX is known to have a strong inhibitory effect on folate metabolism and DNA synthesis, special attention should thus be paid to the occurrence of myelosuppression. The rate of myelosuppression has been reported to be about 10% whereas that of pancytopenia is as low as 1%–2%, and such occurrences are normally followed by a nonfatal outcome.[1] We searched for any reports on the side effects of MTX on MEDLINE CD-ROM including all reports up until the end of 2000. As a result, we found 99 cases of MTX-induced pancytopenia in the English literature starting with MacKinnon's first report in 1985. The authors indicated that the most important factor regarding the occurrence of pancytopenia is renal impairment.[1] In addition, trimethoprim-sulfamethoxazole (TS) and salazosulfapyridine (SASP), which are both folate metabolism blockers, were found to be cofactors for pancytopenia.[1] However, no specific causes have yet been indicated in the majority of patients. In serious cases, bleeding and infection were followed by multiple organ failure as well as disseminated intravascular coagulation (DIC). Surprisingly enough, as few as two administrations of MTX have been reported to cause fatal pancytopenia.[2] The death rate of pancytopenia patients was reported to be 17% by Gutierrez-Urena et al. (USA: MEDLINE search),[2] 30% by Schroder et al. (Germany),[3] and 24% by Berthelot et al. (France).[4] We found 25 cases of death among 99 pancytopenia cases (25%) up until the end of 2000.[5] Although reports in German and French as well as several languages with English abstracts are covered in the MEDLINE CD-ROM, no Japanese journals are included.

Next, we searched through the Japana Centra Revuo Medicina CD-ROM for any reports on MTX-induced pancytopenia; 43 cases were found in the Japanese literature, with 5 reported deaths and 28 recovered cases. The death rate is 16% (Table 1). The rate of pancytopenia in the Japanese literature from six university hospitals was 6/801, 7/297 from national hospitals, prefectural hospitals, and company hospitals, and 4/201 from three private hospitals. Overall, pancytopenia was observed in 17 of 1297 patients at a rate of 1.31%.

The appearance of pancytopenia has been classified into three patterns. The first is a sudden onset of pancytopenia right after MTX therapy is started, based on the presence of renal impairment. The second is observed during the maintenance period of MTX treatment, without identifying common causes except for TS or SASP. The third results from dosage errors such as mistakenly taking a MTX weekly dose every day or a monthly dose in 1 day. In the English literature, nine dosage error cases, have been reported with three deaths.

In the Japanese literature, three cases with the first pattern have been reported in patients on hemodialysis. Three more cases were reported to occur 3–8 weeks after MTX initiation, most likely because of renal impairment. However, no pancytopenia cases due to either TS or SASP have yet been reported. Treatment for pancytopenia consists of administration of Leucovorin, platelet-rich plasma, and G-CSF in Japan. Generally, bone marrow recovery is observed within a week followed by a return to the baseline levels within 2–4 weeks. In a few cases, methylprednisolone is administered to coexisting MTX-induced pneumonitis but not to myelosuppression.

Correlations between serum creatinine (Cr) levels and the MTX administration period were analyzed in patients reported in the English literature by a cluster analysis using a statistical software package, JMP (SAS Institute, NC, USA). An abrupt onset of pancytopenia followed by death is common in patients with renal impairment. Regarding

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Table 1. MTX-induced pancytopenia reports in the Japanese literature

No.	Age	Sex	MTX (mg/week)	MTX (weeks)	Cr (mg/dl)	WBC /μl	Hb (g/dl)	Pl (10^4/μl)	Outcome and days for BM recovery or death		Year	Author[a]	Total cases	· Symptom: treatment [cause of death]
1	48	F	5–7.5	37	1.4	2800	7.2	4.3	Alive	7	1992	Fukui		· pneumonitis: mPSL, FA
2	54	F	2.5–5	3	3.4	200	4.4	1	Died	14	1992	Kamei		: Lv, G-CSF [brain hemorrhage]
3	76	F	7.5	7							1992	Kimura	14	
4	68	F	1.3	24		1000	5	1	Alive	4	1993	Nonaka	53	* previous gastrectomy: FA
5	57	F	5	24	n.r.	300	5.4	2.9	Died	6	1993	Tayama	10	: BT, G-CSF [intraperitoneal hemorrhage]
6	6	M	5–7.5	52	1.1	2400	3.9	8.5	Alive	5	1994	Wada		: CAPD, G-CST
7	65	F	7.5		Up				Alive		1995	Nishitani		
8	61	F	15		Up				Alive		1995	Nishitani		
9	62	M	5–7.5	12	0.9	2400	7.8	15.1	Died	7	1996	Kitsuwa		· penumonitis, *Pn. carinii*: G-CSF [infection]
10	60	F	7.5	29		3479	6.8	3.9	Alive	Promptly	1996	Mino		· pneumonitis: mPSL
11	55	F	5	12	1	600	RBC241	0.3	Alive		1996	Ishikawa		· sepsis of *Ps. aeruginosa*: G-CSF, Lv, mPSL
12	55	F	7.5	12		2000	3.9	3.3	Alive	10	1996	Ishii		* restart at 5 mg after 5 months
13	72	F	1.3–3.8	8	1.4	500			Alive	14	1997	Oyama	103	: mPSL, γ-globulin
14	62	F	5	2	1.3	2100	7.9	4.3	Alive	9	1997	Ohosone	284	: FA
15	81	F	10	32	1.1	1100	3	2.3	Alive	7	1997	Ohosone		: erythropoietin, Lv, BT
16	73	F	5	120	1.3	1600	7.5	4.3	Alive	14	1997	Ohosone		: G-CSF, Lv, BT
17	69	F	5	132	0.4	1500	7.1	4.2	Alive	9	1997	Ohosone		: G-CSF
18	65	F	7.5	12	1.5	300	7	3.8	Alive		1997	Ebisawa		* poor compliance: Lv, G-CSF
19	46	F	5	2 HD	9.8	200	3.8	3.5	Alive	12	1998	Makibayashi		: BT, G-CSF
20	49	F	2.5	2 HD	6	300	5.8	1.3	Alive	19	1998	Makibayashi		: BT, LV, G-CSF
21	57	M		2 HD		100	RBC284	0.2	Alive	14	1998	Nakamura		: G-CSF
22	75	F		16					Died		1998	Suzuki	98	· pneumonitis [bleeding]
23	61	F	7.5	200	0.7	2900		10	Died		1998	Mukai		· *L. monocytogenesis* sepsis and meningoencephalitis, DIC [infection]
24	67	M	5	22	0.5	900	6.8	3.4	Alive	14	1999	Hamada		* complicated malignant lymphoma · pneumonitis
25	74	F	5	24	1.1	1200	6.2	0.4	Alive		2000	Usui		* followed by aplastic anemia
26		1 case									2000	Miyashita	58	
27–32		6 cases							Alive	3–18	2000	Sawai		
33–37		5 cases									2000	Matsui		
38–40		3 cases									2000	Sakuma	77	
41–43		3 cases							Alive	−14	2000	Hayakawa	51	

MTX, methotrexate; BM, bone marrow; n.r., in normal range; HD, hemodialysis; mPSL, methyprednisolone pulse therapy; FA, folic acid; BT, blood tranfusion; Lv, leucovorin; *, exceptional comments

[a] References are preceded by case numbers

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correlation between the occurrence of pancytopenia and MTX administration period, many cases without renal impairment have been observed in which the MTX administration period was longer than a year. Unfortunately, the causes for pancytopenia in these cases were not indicated in any of these reports. In the Japanese literature, the Cr levels in cases 5, 9, 17, and 24 were <1.0 mg/dl, thus indicating the absence of renal impairment (see Table 1).

Consequently, the rate of pancytopenia in RA patients taking MTX and the death rate in pancytopenia patients in the Japanese literature were found to be similar to those in the English literature. However, we should pay close attention to the abrupt onset of pancytopenia during MTX treatment, because deaths are not always willingly reported out of fear of being blamed for a medical mistake. Furthermore, sufficient information on the action and side effects of MTX as well as the correct dosage schedules should also be clearly provided to all patients receiving MTX.

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