Severe myelotoxicity in rheumatoid arthritis patients treated with oral methotrexate

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Treatment of rheumatoid arthritis (RA) with low dose methotrexate (MTX) (5 - 20 mg/weekly) is widely recognized as an effective therapy either alone or combined with other slow-acting antirheumatic drugs. However, up to 55% of RA patients in treatment with MTX present some side effects and 25% abandon the treatment due to toxicity (1,2). Hematological toxicity by MTX is relatively common, frequencies of 2% to 20% having been reported in different series (2, 3). Whereas in the majority of cases the toxicity is not serious and is easily reversible, less frequently there is intense cytopenia of one or more hematological series that can be fatal. We performed a retrospective study on RA patients who developed severe myelotoxicity under treatment with weekly low doses of oral MTX, followed at our hospital from 1986 to 2000.

Severe myelotoxicity was considered when 2 or 3 hematological series fell within the 3-4 degree of the WHO scale, elaborated to evaluate toxicity related to chemotherapy (hemoglobin < 70 g/l,leukocytes < 2 10^9 /1, platelets < 50 10^9/1) (4). From a total of 397 patients, 12 that met these criteria were identified. The charts of these patients were reviewed in detail. Their clinical characteristics and analytical variables were compared with those of a control group of 50 randomly chosen RA patients in treatment with MTX, to identify potential risk factors, including doses and duration of treatment with MTX, serum creatinine, AST and ALT concentrations, mean corpuscular volume values, age, and concomitant or multiple comedications. Control analytical tests that had been carried out 20 to 45 days before admission in patients who had toxicity were also studied (Table I).

Three patients were men and 9 were women. The average age was 71.5 years (range 60-82). According to the mentioned criteria, low values of hemoglobin, leukocytes and platelets were seen in 6, 11,and 10 patients, respectively. Bone marrow biopsy, performed in 7 cases, showed hypoplasia of the three series, with megaloblastoid changes and eosinophilia. In each case the myelotoxicity was of sudden onset. The most frequent clinical characteristics were mucositis, diarrhea, respiratory infection and sepsis. In all cases but one, a control blood test carried out between 20 to 45 days before admission had not shown abnormalities. One patient each died from sepsis, upper gastrointestinal bleeding and pneumonia.

Serum creatinine levels in these patients (1.13 ± 0.19 mg/dl) were higher than in the control group (0.92 ± 0.14 mg/dl). 5 patients showed normal renal function with levels of serum creatinine < 1 mg/dl. In all but 1 case the previous corpuscular hematological values had been normal. Other risk factors analyzed were inconstant or absent.

All patients had been treated with low doses of MTX, which were very similar to the control group, and the duration of treatment was even inferior to this group. This observation is in agreement with the general idea that cytopenia is not related either to the present or accumulated dosage of MTX (5). Our results are in accordance with the statement that impairment of renal function predisposes to bone marrow toxicity (6,7). It is of interest that in 5 cases the values of serum creatinine were ≤ 1 mg/dl and only one case had a value >1.4 mg/dl which is considered to be the cut off value for renal failure (8). Nevertheless older age was a constant in our patients. All of them were over 60 years old, and the mean age was greater than in the control group. These findings are in accordance with others in the literature (9, 10).

We conclude that severe hematological toxicity by MTX in RA is sudden and may develop in patients without previous side effects or alterations in hematological control tests. Whereas an impairment of renal function may play a role in toxicity, our study suggests that old age represents another important risk factor. For all the aforementioned reasons, MTX therapy should be restricted to patients with normal renal function, and a careful analysis and follow up should be done on elderly subjects.

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Table I. Comparative analysis of demographic, posologic and analytical data between patients with severe cytopenia and the control group*.

	Patients (n=12)	Control group (n=50)	P values
Age (yrs.)	71.5 ± 8.21	59.38 ± 15.02	0.004
Duration of MTX treatmemt (mos.)	21.17 ± 15.36	26.58 ± 17.61	0.748
Doses of MTX (mg)	8.54 ± 3.28	9.9 ± 3.03	0.097
Hemoglobin (g/l)	125 ± 12	130.7 ± 13.6	0.155
Leukocytes (x 10^9/l)	7.38 ± 2.84	7.32 ± 2.04	0.782
Platelets (x 10^9/l)	229 ± 98.3	237.9 ± 93.9	0.737
Mean corp volume (fl)	91.27 ± 6.77	92.59 ± 5.72	0.605
Creatinine (mg/dl)	1.13 ± 0.19	0.92 ± 0.14	0.001
ALT (U/l)	28.5 ± 14.61	25.79 ± 14.63	0.418

*Analytical data and MTX dosage in the patient group are those of the last clinical revision, before development of cytopenia.