MITOXANTRONE IN SECONDARILY PROGRESSIVE MULTIPLE SCLEROSIS

A series of 18 patients

Maria Belén Montú, Walter Oleschko Arruda, Marcelo de Souza R. de Oliveira, Ricardo Ramina

ABSTRACT - Mitoxantrone hydrochloride (Novantrone®) is an anthracenedione that has been used as one of the latest in a long line of general immunosuppressive agents studied in multiple sclerosis (MS). We reviewed the clinical, laboratory, neuroimaging and echocardiography data of 18 patients from February 2001 to March 2004 out of a total number of 100 patients with definite MS. Fourteen patients were women (77.7%) and four were men. The mean age of the patients was 41.6±10 years old (confidence intervals 95%: 36.4-46.7 years old). The mean duration of disease was 10.5±6.3 years. Fourteen patients had the secondarily progressive form of MS, and four had the relapsing-remitting form. Mitoxantrone is an useful and clinically effective drug in MS and its major limitation is the potential cardiotoxicity due to cumulative dose (140 mg).

KEY WORDS: mitoxantrone, multiple sclerosis, demyelinating disease.

Mitoxantrone na esclerose múltipla secundária progressiva relato de 18 casos

RESUMO - Hidrocloridrato de mitoxantrone (Novantrone®) é um antracenedione utilizado como o agente mais recente de uma longa linha de imunosupressivos gerais estudados em esclerose múltipla (EM). Realizamos revisão de dados clínicos, laboratoriais, de neuroimagem e ecocardiografia de 18 pacientes, no período de fevereiro de 2001 a março de 2004, a partir de um total de 100 pacientes com EM definida. Quatorze pacientes eram do sexo feminino (77,7%) e quatro eram do sexo masculino. A idade média dos pacientes foi 41,6±10 anos (intervalo de confiança 95%: 36,4-46,7 anos). A duração média da doença foi 10,5±6,3 anos. Quatorze pacientes apresentavam a forma secundária progressiva de EM e quatro a forma surto-remissão. O mitoxantrone é uma droga útil e clinicamente eficaz, sendo a principal limitação sua potencial cardiotoxicidade devido à dose cumulativa (140 mg).

PALAVRAS-CHAVE: mitoxantrone, esclerose múltipla, doença desmielinizante.
in kidney failure or chronic pyelitis patients, diseases that might occur in MS patients, since it is preferably eliminated through the biliary tract.

We reviewed the use of MX in 18 patients out of a series of 100 patients with MS treated at the Instituto de Neurologia de Curitiba (INC).

**METHOD**

Eighteen patients under treatment with MX at the INC were followed from January, 2001 until March, 2004. Fourteen were female and four male (sex proportion 3:1). Their mean age was 41.6±10 years (range 30-61 years). RRMS was the clinical form in 4 cases (22.2%), and SPMS with relapses in 14 subjects (77.7%). Except for two patients (11.1%), who showed intolerance to interferons, the other 16 (88.8%) presented significant neurological worsening at the moment of MX indication in spite of several different implemented therapies in all of them. At the time of MX administration, disease duration ranged between 3 to 20 years (mean = 9.8±5.9 years). Patients were submitted to different cycle intervals of intravenous administration. The cycle followed 120, 90 and 30 days intervals according to the clinical response and side-effects. Twelve cases followed a 90 days interval; two patients alternated 90 and 60 days courses; another one performed three cycles of 90 days, 3 cycles of 120 days and the last 3 cycles of 60 days. One patient received 9 drug administration every 90 days, and the last three followed a 30 days interval course. Two patients received only 2 drug infusions due to severe acute cardiotoxicity (Table 1).

Dosage was also adjusted individually for each patient according to the clinical response and tolerance to the drug infusion. Twelve cases received 12 mg/m², and two cases received 10 mg/m². Two patients were started on MX with 15 mg/m² and gradually lowered to 12 and 8 mg/m². One patient started with 15 mg/m² and was then kept with cycles of 8 mg/m². One last patient was started with 10 mg/m² and afterwards increased to 15 mg/m². The number of drug administration ranged from 1 to 10. Three patients stopped MX after reaching the cumulative maximum dosage (100, 111, 140 mg/m², respectively).

Fourteen cases (77.7%) showed side-effects with mild gastrointestinal symptoms (e.g. nausea, intestinal constipation) that spontaneously receded. One patient (5.5%) presented alopecia and two patients developed acute severe cardiotoxicity (severe ejection fraction decrease), after 1 and 2 MX injections. One patient developed amenorrhea after a sole application. This patient developed acute myeloblastic leukemia after 30 months (case report, in print).

Laboratorial tests (haemogram, liver function, kidney function and platelets) and bidimensional echocardiogram were performed each MX administration. Eight patients showed significant gait and sensorial symptoms improvement. Another 8 patients did not notice any significant symptomatic improvement but remained clinically stable (two of them decided to stop treatment). Nevertheless, 16 cases (88.8%) showed relapses decrease, and disease was stabilized no EDSS change in all 14 SPMS. In fact, no progression of EDSS of at least one point was found in any patient.

Cardiac ejection fraction (EF) decrease was observed in all cases, but only two registered values below normality (<55%); though they were asymptomatic, treatment was immediately stopped in these two cases and follow-up echocardiogram showed EF return to normal values.

**DISCUSSION**

Several studies showed that immune-mediated suppression of inflammatory process can lessen the number of relapsing events or progressive clinical worsening in MS. Unfortunately, neurological function progressive loss cannot be arrested, since pa-

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age (years)</th>
<th>Clinical form</th>
<th>MX total dosage mg/m²</th>
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<td>50</td>
<td>SP*</td>
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<tr>
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\[ \bar{x} \pm SD = 41.5 \pm 10 \quad 68.6 \pm 33.3 \]

* RR, relapsing-remitting; SP, secondarily progressive.
thological studies had already revealed axonal damage and neuronal degeneration as important mechanisms that occur in progressive MS1,9,20.

MX therapy should be considered in MS patients with RR or SP forms, when inflammatory process still has an important role in disease pathogenesis (e.g. presence of active lesions in MRI). The objective is to lessen the neurological disability period, since there is no effective therapy that can retrieve the axonal and neuronal destructive process of this demyelinating disease21.

In Oregon, a trial was performed by Touchette et al.22, comparing IV MX with interferonb-1a during 10 years, and showed a higher efficacy and lower cost with MX usage.

In conclusion, MX is a cytotoxic agent with high anti-inflammatory effect which shows good efficiency and tolerance in treating RRMS and SPMS patients, with neurological worsening, based on present literature data and in our series. MX has proved to be a safe and well-tolerated drug that might be indicated in RRMS and SPMS. The cycle interval may be adapted accordingly to individual patient response to its use. In spite of the variable dosage per square meter body surface, it is probably advisable to keep the usual dosage of 12 mg/m2, for there is no current evidence based on controlled studies that the use of lower or even higher dosage might be safer and more effective, respectively. One may propose the use of MX at the early stages of the disease (in the RR phase) in patients with very active disease demonstrated by number of relapses and/or number of active lesions on MRI, to rapidly decrease the inflammatory process and thus decrease the potential risk of major disabilities. In a posterior phase of the disease and depending upon the response to this treatment, MX could be stopped or kept in addition or be substituted by the use of an immunomodulatory drug. In fact, there are already some open label trials involving RRMS and SPMS patients treated with a combination of MX and interferon β-1a or β-1b or glatiramer acetate.

The major disadvantage of MX is its potential cardiotoxicity due to the cumulative dosage. One way to circumvent this problem might be the use of other immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, methotrexate) plus an immunomodulatory drug21.

REFERENCES