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MITOXANTRONE IN SECONDARILY PROGRESSIVE MULTIPLE SCLEROSIS

A series of 18 patients

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ABSTRACT - Mitoxantrone hydrochloride (Novantrone®) is an anthracenedione that has been used as one of the latest in a long line of general immunosuppresive 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 potencial 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 imunossupressivos 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.

Mitoxantrone hydrochloride (Novantrone®) is an anthracenedione or cytotoxic agent used for several malignant disorders treatment[1-3]. Its usage has been approved by Food and Drug Administration (FDA) for the treatment of patients with relapsing-remitting multiple sclerosis (RRMS) showing exacerbations that provoke severe and permanent sequelae, patients in secondary progressive phase presenting worsening in one or more points per year in Expanded Disability Status Scale (EDSS), and those who do not respond to other therapeutical strategies[3-12]. In fact, benefit can be seen in disease progression in patients with secondary progressive MS (SPMS)[13-15]. Randomized studies has also showed reduction of relapsing and new lesions incidence using magnetic resonance imaging (MRI)[16-18].

Mitoxantrone (MX) acts as an immunosupressive agent which alters B and T lymphocytes responses to central nervous system (CNS) antigens, and through this process it seems to avoid axonal lesion and macrophages mediated demyelination[1-9,13,19]. After 14 days, white blood cells counting is lowered at a significant level, firstly affecting neutrophils and the majority of lymphocytes, excepting Th_0 and activated T cells[14]. It can be administered

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in kidney failure or chronic pyelitis patients, diseases that might occur in MS patients, since it is preferrably 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/m^2, and two cases received 10 mg/m^2. Two patients were started on MX with 15 mg/m^2 and gradually lowered to 12 and 8 mg/m^2. One patient started with 15 mg/m^2 and was then kept with cycles of 8 mg/m^2. One last patient was started with 10 mg/m^2 and afterwards increased to 15 mg/m^2. The number of drug administration ranged from 1 to 10. Three patients stopped MX after reaching the cummulative maximum dosage (100, 111, 140 mg/m^2, respectively).

Fourteen cases (77.7%) showed side-effects with mild gastrointestinal symptoms (e.g. nausea, intestinal constipation) that spontaneously receeded. 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 supression 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 1. MX treated patients.

Patient	Gender	Age (years)	Clinical form	MX total dosage mg/m^2
1	female	50	SP*	111
2	female	38	SP	48
3	female	61	SP	90
4	female	34	SP	60.4
5	female	47	SP	12
6	female	31	SP	140
7	female	41	SP	46
8	female	53	SP	76
9	female	53	SP	106.3
10	female	47	SP	60
11	male	30	SP	30
12	male	28	SP	71.8
13	male	40	SP	68.9
14	male	39	SP	100
15	female	35	RR*	82
16	female	44	RR	60
17	female	33	RR	57.6
18	female	23	RR	15
$_0\overline{X}$ ± SD	-	41.5±10	-	68.6±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 MS[3,9,20].

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 disease[21].

In Oregon, a trial was performed by Touchette et al.[22], comparing IV MX with interferonb-1β 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/m^2, 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 cummulative dosage. One way to circumvent this problem might be the use of other immunosuppressive drugs (e.g. cyclophosphamide, azathioprine, methotrexate) plus an immunomodulatory drug[21].

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