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ORIGINAL COMMUNICATION

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Sequential maintenance treatment with glatiramer acetate after mitoxantrone is safe and can limit exposure to immunosuppression in very active, relapsing remitting multiple sclerosis

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Abstract Mitoxantrone has been approved by the FDA for worsening relapsing remitting and secondary progressive Multiple Sclerosis. However the benefits of this agent in reducing disease progression and relapse rate cannot be sustained in the long-term, as treatment is limited by the potential for cumulative cardiotoxicity. We report our experience utilising Glatiramer Acetate as maintenance immuno-modulatory treatment following initial immunosuppression with Mitoxantrone in a consecutive series of 27 patients with very active relapsing remitting disease, eight of whom had experienced continuing relapse activity on first-line treatment. Duration of treatment with Mitoxantrone and thereby cumulative dose were reduced as our experience with the combination increased.

No unanticipated side effects of combination treatment were encountered over a follow-up period of 66 months. A single patient developed therapy related acute leukaemia (TRAL) 9 months after completion of Mitoxantrone.

A sustained 90% reduction in annualised relapse rate ($p < 0.001$) has been observed. Disability is stable or improved in all patients a mean of 36 (16–66) months from initiation of treatment. Early suppression of relapse activity with Mitoxantrone has been maintained at a mean of 22 months from last dose of this agent. Only two relapses have occurred in the cohort since withdrawal of Mitoxantrone, occurring in the two patients who had previously been treated with Glatiramer Acetate. In 9 of the first 10 patients treated, imaged a mean of 27 months after withdrawal of Mitoxantrone, no enhancing lesions were identified on MRI brain scans.

Glatiramer Acetate appears a safe and effective option for continuing disease modification in patients with relapsing remitting multiple sclerosis treated with Mitoxantrone. The treatment protocol utilised in later patients in this series appears to have the potential to limit exposure to this agent.

Key words very active multiple sclerosis · mitoxantrone · glatiramer acetate · combination therapy

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Introduction

As a result of positive outcomes in a series of randomised controlled trials [1, 2, 4] Mitoxantrone has become the first immunosuppressive agent to be licensed for the treatment of multiple sclerosis (MS), with the indications in the United States specifying 'worsening' relapsing remitting (RR) or secondary progressive MS. The use of mitoxantrone is, however, limited to a lifetime maximum dose of 140 mg/m^2 by its potential to cause cumulative cardiotoxicity. In those patients whose disease stabilises with mitoxantrone an early switch to an alternate disease-modifying drug is therefore desirable; however, the most appropriate choice of therapy for maintenance of remission remains uncertain.

Having used Mitoxantrone in very active RRMS since 1997, following the publication of the study by Edan et al. in this patient group [2], we have developed a protocol for the subsequent use of glatiramer acetate (GA) as a long-term disease-modifying agent following treatment with mitoxantrone. This paper presents a retrospective review of the first twenty-seven consecutive patients treated in this manner.

Patients and methods

Twenty-seven patients were treated with mitoxantrone followed by GA. All patients had clinically definite multiple sclerosis with a disease duration of less than five years from onset. Inclusion criteria for treatment, which were predetermined, reflected factors known to be associated with high risk of early disability [3]. These included at least two of the following: two or more steroid treated motor relapses in the last twelve months, residual disability from relapses as determined by serial expanded disability status scores (EDSS) and high MRI lesion load, usually reflected by 10 or more lesions on T2 weighted brain images.

In 19 patients mitoxantrone was used as 'first-line' treatment because of the apparent aggressive nature of the disease. The remaining eight patients had experienced continuing relapse activity despite treatment with initial disease modifying therapy (DMT), six on Interferon Beta and two on GA, for a mean of 8.75 months (range 2–21).

Mitoxantrone was administered intravenously as a day case procedure. The first four patients received 20 mg monthly mitoxantrone for six months accompanied by 1 g methylprednisolone, following the protocol of Edan et al. [2] subsequently 10 mg mitoxantrone was administered at three monthly intervals. In the next six patients the dosage was reduced in the light of additional trial data [4] and patients received 20 mg for three consecutive months with subsequent pulses of 10 mg given every three months. When patients became clinically stable, without relapses or worsening of expanded disability status scale (EDSS) for a period of 6 months, GA (20 mg, sc, daily) was introduced while patients received one or two further pulses of mitoxantrone. The two drugs were administered simultaneously for at least two months. Treatment with mitoxantrone was then withdrawn.

The treatment protocol evolved with experience and the publication of additional data [4], with duration of treatment with mitoxantrone being gradually reduced in the first 10 patients. The protocol was then standardised in the remaining 17 patients, each patient receiving 5 pulses of mitoxantrone. In these patients treatment was administered at monthly intervals for the first 3 months and three monthly intervals for the last two (months 0, 1, 2, 5 and 8). GA was initiated between third and fourth pulses of mitoxantrone.

Patients were reviewed clinically at six monthly intervals with assessment of disability, as measured by EDSS, and at times of apparent relapse. Full blood count, routine biochemistry and liver function were undertaken prior to each infusion. Trans-thoracic echocardiogram was repeated in the early patients who received a cumulative dose of 100 mg of mitoxantrone and then six monthly if continuing on treatment.

In nine of the first 10 patients, standardised MRI of the brain was undertaken (Siemens 1.5 Tesla Magnetom 63SP) using T2 axial, proton density axial and T1 axial (pre- and post- intravenous gadolinium contrast) a mean of 27 months after withdrawal of mitoxantrone. One patient declined MRI because of to claustrophobia. The scans were reviewed by an independent neuroradiologist (KD).

Results

Patient characteristics, treatment parameters and clinical results are given in Table 1. Figure 1 annotates steroid treated relapses documented in this patient cohort prior to treatment with mitoxantrone, on mitoxantrone and GA and on GA alone.

Mean follow-up period since first treatment with mitoxantrone is currently 36 (16–66) months. The mean total dose of mitoxantrone was 74 (45–125) mg/m^2 for the first 4 patients, 54 (45–74) mg/m^2 for next 6 patients and then 48 mg/m^2 for the remaining 17 (standard protocol).

The mean annualised relapse rate (ARR) in the 2 years preceding treatment with mitoxantrone was 2.7 reducing to 0.106 following treatment. Statistical analyses were performed using paired Student's t-test. There was a significant reduction in ARR (mean difference was 2.594, 95% CI 1.79–3.40, $p<0.001$). There were five motor relapses, all confirmed by the treating physicians, requiring steroid treatment during the mitoxantrone induction period. One further sensory relapse, nor requiring treatment, occurred in this period. There have been only 2 relapses on GA alone. Of note, the 2 relapses on GA alone occurred in the two patients who had experienced continuing relapse activity on GA given as first line treatment. The median EDSS pre-treatment was 5.5. This has reduced to 4.0 at the most recent follow-up. In this cohort of patients, however, the pre-treatment EDSS was often recorded during recovery from relapse, as treatment with mitoxantrone was initiated, and cannot therefore be regarded as a stable baseline.

Dose related leucopenia was noted in three patients, recovering with reduction in dosage; in all three patients the dosage was halved on one occasion – in accordance with our local protocol – because of white cell counts of between 2–4 × 109/l. Transient amenor-

Table 1 Patient characteristics, treatment details and clinical outcomes (* After 11 months on GA alone, patient 10 stopped it because of recurrent erythematous injection site reactions). MX - Mitoxantrone, GA- Glatiramer acetate, EDSS- Expanded Disability Status Scale, DMT – Disease Modifying Therapies

No. of Pts.	Age	Sex	DMT Pre-MX	Cumulative dose of MX in mg (mg/m2)	Time since MX started (mths)	Time on GA alone	ARR 2 years pre-MX	ARR post-MX	Pre-Mx EDSS	Current EDSS
1	44	F	-	190 (114)	66	37	2.0	0	6.0	5.5
2	35	M	-	170 (102)	61	40	2.0	0	6.0	1.5
3	24	F	Int	160 (96)	59	39	3.7	0.2	6.5	2.0
4	32	M	Int	180 (108)	59	34	3.1	0.2	6.0	5.5
5	46	M	-	100 (60)	59	37	2.0	0	6.0	4.5
6	36	M	-	130 (78)	57	32	4.5	0.2	3.5	2.5
7	40	M	-	120 (72)	57	36	1.5	0	6.0	3.5
8	42	F	-	90 (54)	47	36	9.0	0	4.5	1.0
9	28	M	-	110 (66)	49	39	1.5	0	5.5	1.5
10	32	M	-	90 (54)	44	11*	3.4	0	3.5	1.5
11	26	M	-	80 (48)	35	26	4.0	0	5.5	5.0
12	31	F	-	80 (48)	57	48	2.0	0	6.5	6.0
13	25	F	-	80 (48)	32	21	8.0	0	5.5	1.0
14	24	F	-	80 (48)	29	20	2.4	0	6.5	6.0
15	18	F	-	80 (48)	24	15	1.6	0	6.0	4.5
16	33	F	Int	80 (48)	39	30	1.5	0	5.0	4.0
17	40	F	Int	80 (48)	21	12	1.0	0	5.5	4.5
18	43	F	Int	80 (48)	21	12	1.0	0	5.5	5.0
19	26	F		80 (48)	20	11	4.8	0	2.0	1.0
20	39	F	-	80 (48)	19	10	1.0	0	4.5	3.0
21	31	F	-	80 (48)	19	10	2.8	0	5.5	3.5
22	17	F	GA	80 (48)	18	9	1.0	0.75	6.0	6.0
23	24	M	-	80 (48)	17	8	1.2	0	5.5	4.0
24	51	F	Int	80 (48)	17	8	1.5	0.75	6.0	4.5
25	31	F	-	80 (48)	17	8	2.0	0	6.0	4.0
26	31	F	GA	80 (48)	17	8	2.0	0.75	5.0	4.0
27	31	F	-	80 (48)	16	7	2.4	0	5.5	4.5
Mean	33	9M/18F	8 on DMT	Mean: 100 mg/60 mg/m2	36	22	2.7	0.106	Median: 5.5	Median: 4.0

rhoea occurred in one patient. In this individual menstruation re-commenced 8 months after withdrawal of mitoxantrone. On serial trans-thoracic echocardiograms none of the patients receiving 100 mg or more of Mitoxantrone were found to have a reduced ejection fraction (>10% reduction or LVEF <50%).

Therapy related acute leukaemia (TRAL) occurred in one patient who developed acute promyelocytic leukaemia seven months after stopping mitoxantrone. He had received a cumulative mitoxantrone dose of 110 mg (66 mg/m^2). The leukaemia is in remission 12 months after diagnosis, his MS has been stable and the patient remains relapse free to date.

A further patient (patient 10) stopped GA after 11 months because of recurrent erythematous injection site reactions. This patient has remained relapse free, off all treatment, for a further 26 months. No unanticipated side effects were seen; in particular patients tolerated simultaneous treatment without incident.

MRI comparisons with pre-treatment imaging are limited by the non-standardised nature of the pre-treatment scans; however, there was an overall decrease in brain T2 lesion number and corresponding reduction in lesion volume. On current imaging (9 patients) no gadolinium enhancing lesions were identified.

Discussion

We report our experience with a treatment regime which maintains immuno-modulation with GA after treatment with mitoxantrone in a series of patients with very active RRMS. The prompt reduction in relapse activity, by greater than 90% (ARR reduced from 2.7 to 0.106) following initiation of mitoxantrone in this cohort, mirrors that reported in randomised controlled studies [1,2,4] and confirms the profound anti-inflammatory activity of this agent in active RRMS.

The cumulative side-effect profile of mitoxantrone however makes its use problematic in young, fertile patients with MS. Treatment protocols are needed, which minimise exposure to this agent, and thereby risk, in this patient group. Our use of GA as a follow-up treatment to mitoxantrone was prompted by disappointing experience with interferon beta utilised in a small number of similar patients whose disease had stabilised on mitoxantrone, with relapse activity

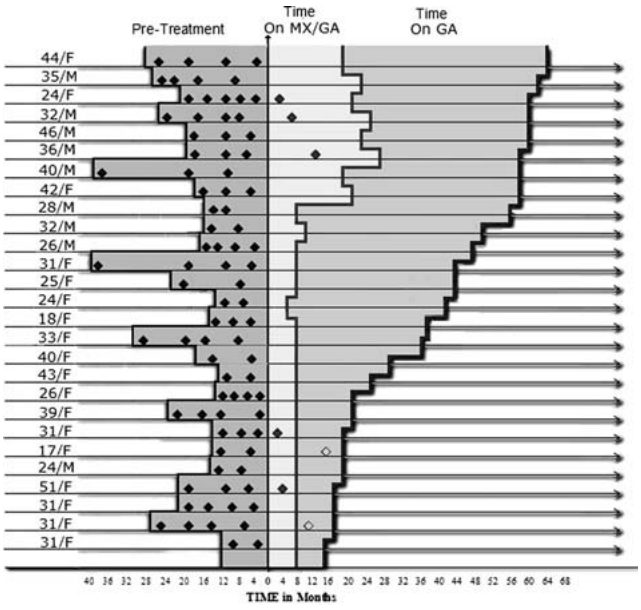

Fig. 1 – **Relapses Pre-, During and Post- Mitoxantrone (MX)** ● - Relapses Pre-MX ● - Relapses During MX ◇ - Relapses Post MX

recurring on Interferon 6–12 months after withdrawal of mitoxantrone. Similar treatment experience has been recently reported by Correale et al. where in 10 patients with very active RRMS, whose disease had stabilised on mitoxantrone, relapse activity recurred in 6 of the 10 patients within 18 months of withdrawal of mitoxantrone despite subsequent treatment with interferon beta [5].

In view of the apparent slow onset of action of GA, occurring over 3–6 months [6], we elected to initiate treatment with GA whilst continuing mitoxantrone for one or two further pulses. Combination treatment was well tolerated and not associated with any adverse events other than those known to be related to mitoxantrone (TRAL, transient amenorrhoea and leucopoenia) or GA alone (injection site reaction), the latter leading to discontinuation of treatment in a single patient.

The single case of TRAL represents the only such case in 120 patients treated with mitoxantrone over the last 8 years in our centre. TRAL, most commonly acute pro-myelocytic leukaemia, has to date been reported in 5 of 2336 MS patients treated with mitoxantrone representing an incidence of 0.21% [7]. It appears to be an idiosyncratic adverse event and in contrast to mitoxantrone related cardiotoxicity is not clearly dose related. No cases have occurred in a post-licencing study of mitoxantrone, involving 500 patients, being undertaken in the United States [8].

To date further clinical relapses have occurred in only 2 of the 27 patients treated with this combination (both of whom had previously experienced continuing relapses on GA alone) and EDSS is stable or improved in all. Follow-up extends to up to 40 months after withdrawal of mitoxantrone, well beyond the likely duration of action of this agent. The absence of gadolinium enhancement on recent imaging in 9 of the first 10 patients, undertaken a mean of 27 (20–31) months following withdrawal of mitoxantrone, would suggest continuing suppression of sub-clinical disease activity.

The profound and apparently sustained effect on relapse activity seen with this novel combination appears greater than that seen with either agent alone; leading us to speculate that the two agents may have a synergistic effect in active relapsing remitting MS. One potential mechanism for such synergy would be transient reduction of Th1 auto-aggressive T-cell lines following pulsed mitoxantrone promoting a more profound and sustained response to GA. However, given the novel chemical structure of GA – a series of randomly assembled poly-peptides derived from the dominant amino-acids of myelin basic protein – it is conceivable that the interaction may reflect auto-immune tolerance as recently demonstrated in a chronic relapsing mouse model of MS [9]. In this model sequential treatment with T-cell depletion, achieved with an anti-CD4 monoclonal antibody or mitoxantrone, followed by re-exposure to myelin antigens induced a complete and sustained inhibition of inflammatory disease activity. Though theoretically mitoxantrone induced inhibition of T-cell function might negatively influence the activity of GA-reactive T-cells the sustained suppression of clinical disease activity in this patient population argues against any adverse interaction.

There are limitations to this open label, uncontrolled data. The treatment protocol was not standardised, later patients receiving smaller doses of mitoxantrone without any apparent change in clinical outcomes. Though we used greater than currently recommended doses of mitoxantrone in our initial patients, based on available evidence at that time, we find it reassuring that no unanticipated side effects were seen. The treatment protocol utilised in the latter 17 patients limits exposure to a maximum of 48 mg/m^2, well within both the American Academy of Neurology guidelines which suggest a maximum dosage of 96 mg/m2 [10] and the approved lifetime maximum dosage of 140 mg/m2.

In conclusion, clinical and MRI outcomes in this series of patients with aggressive RRMS and high risk of early disability are encouraging, with no novel side effects emerging relating to combination treatment. At a mean of over 3 years from initiation of treatment disability is stable or improved and there has been a profound and sustained suppression of relapse activity. Though it seems unlikely that any new side

effects related to the combination will arise at this point, further follow-up of this cohort and subsequent patients is required to assess long-term safety. GA appears to be a safe and potentially effective option for continuing disease modification in those patients with very active RRMS who have been treated with mitoxantrone. An investigator led, multi-centre study in the UK has been initiated to compare this combination with high dose Interferon beta (Rebif 44) in patients with early active RRMS.

References

1. Millefiorini E, Gasperini C, Pozzilli C, D'Andrea F, Bastianello S, Trojano M, Morino S, Morra VB, Bozzao A, Calo' A, Bernini ML, Gambi D, Prencipe M (1997) Randomized placebo controlled trial of Mitoxantrone in relapsing remitting multiple sclerosis: 24 month clinical and MRI outcome. J Neurol 244:153–9
2. Edan G, Miller D, Clanet M, Confavreux C, Lyon-Caen O, Lubetzki C, et al. (1997) Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicentre study of active disease using MRI and clinical criteria. J Neurol Neurosurg Psychiatry 62(2):112–118
3. Scott TF, Schramke CJ, Cutter G (2003) Sample size estimates for determining treatment effects in high-risk patients with early relapsing-remitting multiple sclerosis. Mult Scler 9: 289–292
4. Hartung HP, Gonsette R, Konig N, Kwiecinski H, Guseo A, Morrissey SP, et al. (2002) Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. Lancet 360(9350):2018–2025
5. Correale J, Rush C, Amengual A, Goicochea M (2005) Mitoxantrone as rescue therapy in worsening relapsing-remitting MS patients receiving IFN-beta. J Neuroimmunol 162(1–2):173–83
6. Comi G, Filippi M, Wolinsky JS, European/Canadian Glatiramer Acetate Study Group (2001) European/Canadian Multicenter, Double-Blind, Randomized, Placebo-Controlled Study of the Effects of Glatiramer Acetate on Magnetic Resonance Imaging-Measured Disease Activity and Burden in Patients with Relapsing Multiple Sclerosis. Ann Neurol 49(3):290–297
7. Voltz R, Starck M, Zingler V, Strupp M, Kolb HJ (2004) Mitoxantrone therapy in multiple sclerosis and acute leukaemia: a case report out of 644 treated patients. Mult Scler 10(4):472–4
8. Fox E, Al-Sabbagh A, Bennett R, Sadiq S (2005) Safety and tolerability of Novantrone (mitoxantrone) in clinical practice: status report from the Registry To Evaluate Novantrone Effects in Worsening MS (RENEW) study. Program and abstracts of the American Academy of Neurology 57th Annual Meeting; April 9–16, 2005; Miami Beach, Florida. Abstract S46.008
9. Pryce G, O'Neill J, Croxford J, Amor S, Hankey D, East E, Giovannoni G, Baker D (2005) Autoimmune tolerance eliminates relapses but fails to halt progression in a model of multiple sclerosis. J Neuroimmunol 165(1–2): 41–52
10. Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW (2003) The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 61:1332–1338