Mitoxantrone plus methylprednisolone improved active multiple sclerosis


Objective
To determine the efficacy of mitoxantrone for patients with very active, rapidly progressing multiple sclerosis.

Design
Randomized controlled trial with 6-month follow-up.

Setting
5 university hospitals in France.

Patients
42 patients (mean age 32 y, 62% women) with definite multiple sclerosis (Poser criteria). Inclusion criteria were age between 18 and 45 years, disease duration < 10 years, active disease (either 2 relapses with sequelae within the previous 12 mo or progression of ≥ 2 points on the Expanded Disability Status Scale [EDSS] in secondary progressive disease), ability to walk (EDSS < 6.5), and development of ≥ 1 lesion identified by magnetic resonance imaging (MRI) at baseline. Exclusion criteria were systemic disease, cardiac disease, mental deficit, or recent use of steroid therapy or immunosuppressive agents. Follow-up was 88%.

Intervention
All patients received intravenous methylprednisolone, 1 g/mo and 1 g/d for 3 days for relapses. 21 of 42 patients were allocated to intravenous mitoxantrone, 20 mg/mo.

Main outcome measures
MRI scans were done monthly and read blind. The primary outcome was the development of new confirmed lesions in the previous month. Secondary outcomes were the mean number of new lesions, changes in the EDSS scores, and exacerbations.

Main results
Patients who received mitoxantrone, compared with patients who received no mitoxantrone, developed fewer new lesions at 2, 3, 5, and 6 months (P < 0.05 for all comparisons) (Table), had fewer total lesions at each period (P < 0.05), had fewer exacerbations (7 vs 31, P < 0.01), were more likely to be free of exacerbations (P = 0.03), and had more adverse events (61 vs 11). Differences between the groups for mean EDSS scores occurred only at 4 months, and at 6 months the differences between baseline scores showed less deterioration in the mitoxantrone group (P < 0.01).

Conclusions
Mitoxantrone plus methylprednisolone reduced the number and rate of new confirmed lesions and exacerbations and improved clinical scores in patients with very active multiple sclerosis. Adverse events were increased.

Source of funding: Not stated.


Mitoxantrone vs mitoxantrone plus methylprednisolone for multiple sclerosis*

<table>
<thead>
<tr>
<th>Outcomes at 6 months</th>
<th>Mitoxantrone EER</th>
<th>Mitoxantrone CER</th>
<th>RBI (95% CI)</th>
<th>ABI (EER – CER)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No new lesions</td>
<td>90%</td>
<td>31%</td>
<td>190%</td>
<td>59% (57 to 545)</td>
<td>2 (1 to 3)</td>
</tr>
<tr>
<td>No exacerbations</td>
<td>67%</td>
<td>33%</td>
<td>100%</td>
<td>33% (6 to 307)</td>
<td>3 (2 to 32)</td>
</tr>
</tbody>
</table>

*Abbreviations defined in Glossary; RBI, ABI, NNT, and CI calculated from data in article.

Commentary
Patients with multiple sclerosis who are becoming rapidly disabled by frequent relapses or secondary progressive disease are a great source of distress to most neurologists. This study included patients with aggressive disease as shown by the high rate of relapse and new MRI lesions seen in the control group. Patients with "mental deficits" were excluded. Unfortunately, these deficits were not further defined and this may reduce the generalizability of the study because many patients with aggressive disease have cognitive or emotional impairments or both.

The study provides good evidence that intravenous mitoxantrone reduces disease activity, even within 1 month but particularly after 3 months. However, the primary outcome measure (new lesions detected by MRI assessed by blinded readers) is only a surrogate measure and, although clinical assessments suggested that exacerbations and disability were also reduced, these assessments were unblinded. The risk for bias arising from unblinded assessment even in randomized controlled trials has been shown (1). Furthermore, patients receiving mitoxantrone had more adverse effects and the long-term harm has not been studied. Thus, as with β-interferon, the utility of mitoxantrone in clinical practice is still uncertain. Nonetheless, this study of an important clinical problem suggests that more aggressive treatment with immunomodulatory drugs might offer clinical benefits to patients with rapidly progressing multiple sclerosis, but the evidence is not yet sufficient to warrant this treatment outside the context of further clinical trials.

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Reference
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