Mitoxantrone slowed progression of disability and reduced relapses in multiple sclerosis

Hartung HP, Gonsette R, König N, et al. **Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial.** Lancet. 2002;360:2018-25.

QUESTION
In patients with worsening relapsing–remitting or secondary progressive multiple sclerosis (MS), is mitoxantrone effective for slowing progression of disability and reducing relapses?

DESIGN
Randomized (allocation concealed*), blinded (patients and outcome assessors),* placebo-controlled trial with 24-month follow-up.

SETTING
17 centers in Belgium, Germany, Hungary, and Poland.

PATIENTS
194 patients 18 to 55 years of age who had worsening relapsing–remitting or secondary progressive MS. Additional inclusion criteria included Kurtzke Expanded Disability Status Scale (EDSS) score 3.0 to 6.0 and worsening by ≥ 1 EDSS point during the 18 months before enrollment. 188 patients (97%) (mean age 40 y, 52% women) completed follow-up.

INTERVENTION
Patients were allocated to mitoxantrone, 12 mg/m^2 (n = 63), 5 mg/m^2 (n = 66), or placebo (n = 65) administered intravenously every 3 months for 24 months. By design, only patients in the mitoxantrone 12-mg and placebo groups were included in the primary analysis.

MAIN OUTCOME MEASURES
The primary outcome was a composite of 5 clinical measures, including change from baseline EDSS at 24 months, change from baseline ambulation index at 24 months, number of relapses treated with corticosteroids, time to first treated relapse, and change from baseline standardized neurologic status at 24 months, tested in 1 combined hypothesis of stochastic ordered alternatives.

MAIN RESULTS
Analysis was by intention to treat. Progression of disability was slower, and number of relapses fewer in the mitoxantrone 12-mg group than in the placebo group (assessed on the composite outcome as well as on the individual components) (Table).

CONCLUSION
In patients with worsening relapsing–remitting or secondary progressive multiple sclerosis, mitoxantrone was effective for slowing progression of disability and reducing relapses.

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*See Glossary.

Mitoxantrone (12 mg/m^2) vs placebo in relapsing–remitting or secondary progressive multiple sclerosis at 24 months†

Outcomes	Mitoxantrone	Placebo	Mann–Whitney difference (95% CI)	P value‡
Global difference in composite outcome	—	—	0.30 (0.17 to 0.44)	< 0.001
Mean change from baseline in EDSS score	−0.13	0.23	0.24 (0.04 to 0.44)	0.019
Mean change from baseline in AIN score	0.30	0.77	0.21 (0.02 to 0.40)	0.031
Mean change from baseline in SNS score	−1.07	0.77	0.23 (0.03 to 0.43)	0.027
Number of treated relapses	24.08	76.77	0.39 (0.18 to 0.59)	< 0.001
Median time to first treated relapse (mo)	N/R	14.19	0.44 (0.20 to 0.69)	< 0.001

†AIN = ambulation index; EDSS = Expanded Disability Status Scale; N/R = not reached in 24 months; SNS = standardized neurologic status; composite outcome = EDSS, AIN, SNS, number of treated relapses, and time to first treated relapse. CI defined in Glossary.
‡All significant differences favor mitoxantrone.

COMMENTARY

Current MS treatments have limited effect on patients who have entered a progressive phase of the disease. Therefore, a promising new therapy evokes great interest and explains the early release of such a drug for the treatment of these patients. The well-designed, industry-funded trial by Hartung and colleagues shows that mitoxantrone can slow the progression and reduce the number of relapses over a 2-year period. This finding may provide an option when first-line disease-modifying drugs, β-interferons and glatiramer acetate, fail or are inadequate. It would be most important to have an effect on progression of MS, but the effect in this study was greater on relapses ($P < 0.001$) than on progression ($P = 0.019$ for EDSS, and $P = 0.031$ for the ambulation index).

Despite some initial enthusiasm in the MS community for the early trial results of mitoxantrone, there are serious limitations to the use of this drug. First, the therapeutic effect is modest. It has substantial but manageable side effects during the infusions. Second, serious dose-related cardiac effects limit its use to about the 24 months covered by this trial.

The cardiac effects can be permanent, and patients must have cardiac monitoring of ejection fraction and other variables before and during treatment. Thus, selection and supervision of patients undergoing therapy should be done by an experienced neurology and cardiology team.

Although the authors have shown benefit in the 2 years when the drug can be used, what happens next? Does this short-term therapy have worthwhile long-term benefit? Once the dose limit has been reached or serious cardiac effects have developed, what do we have to offer the patient? MS is a chronic disease, and the long-term benefit of a partially effective, potentially toxic, short-term treatment requires evaluation beyond a 24-month clinical trial. A minimum suggestion would be to follow all patients in this trial annually to determine the time-to-wheelchair to see if the limited course of therapy has any lasting worthwhile effect.

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