

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

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Abstract—Mitoxantrone is the first drug approved for the treatment of secondary progressive multiple sclerosis (SPMS) in the United States. This assessment considers use of mitoxantrone in the treatment of MS. Mitoxantrone probably reduces the clinical attack rate and reduces attack-related MRI outcomes in patients with relapsing MS (Type B recommendation). Also, mitoxantrone may have a beneficial effect on disease progression in patients with MS whose clinical condition is worsening (Type B recommendation). The potential for serious toxicity of mitoxantrone, however, must be taken into account when considering this therapy in individual patients. Moreover, because the potential clinical benefits on disease progression appear to be only modest, the results of the single phase III trial should be replicated in another (and hopefully much larger) clinical study before this agent is widely recommended for the treatment of patients with MS.

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Mitoxantrone hydrochloride (Novantrone) is an anthracenedione that has been used as an antineoplastic agent to treat hormone-refractory prostate cancer and acute nonlymphocytic leukemia in adults. It exerts its antineoplastic action by intercalating into DNA and producing both DNA strand-breaks and interstrand cross-links; it also interferes with RNA synthesis and markedly inhibits the enzyme topoisomerase II, which aids in the DNA repair process.¹⁻⁴ In the treatment of MS, mitoxantrone represents the latest in a long line of general immunosuppressive agents studied in this disease. Previously, most such agents have not shown clear-cut benefits in this condition.⁵⁻¹⁰ On the basis of a phase III clinical trial in Europe,^{11,12} and an earlier phase II study,¹³ mitoxantrone recently received an expanded indication from the Food and Drug Administration (FDA) for use in secondary progressive MS (SPMS), in progressive-relapsing MS, and for patients with worsening relapsing-remitting (RR) MS. This last category is defined as patients whose neurologic status remains significantly abnormal between MS attacks.

Mitoxantrone is the first drug approved for these indications in the United States, and it is the purpose of this assessment to consider both the evidence leading to the recent FDA approval as well as the appropriate clinical role of this agent in the management of patients with MS.

Description of the analytic process. Articles for this review were searched in Medline under the keywords mitoxantrone and MS. Forty-one articles were identified by this search. The abstracts of these articles were reviewed and the original articles were selected for inclusion in the analysis only if they were either controlled trials or case series using mitoxantrone in the treatment of MS. Five such articles were identified, in addition to the phase III trial.^{11,12} In addition, the reference lists of the articles found in this manner were also reviewed to identify articles or abstracts not found by the computer search.

Analysis of the evidence. Following its successful use in the treatment of experimental allergic encephalomyelitis,^{14,15} mitoxantrone was initially studied in an open label, single arm pilot trial (Class IV evi-

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The University of California, San Francisco is participating in a clinical trial of mitoxantrone in the treatment of primary progressive MS (PI: S. Zamvil). D.S.G. is a participating investigator (without salary) in that trial, which received \$161,900 in appropriations from Immunex.

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Table Rating of Evidence Classification Scheme

Rating of recommendation	Translation of evidence to recommendations	Rating of Therapeutic Article
A = Established as effective, ineffective, or harmful for the given condition in the specified population.	Level A rating requires at least one convincing class I study or at least two consistent, convincing class II studies.	Class I: Prospective, randomized, controlled clinical trial with masked outcome assessment, in a representative population. The following are required: <ol style="list-style-type: none"> primary outcome(s) is/are clearly defined exclusion/inclusion criteria are clearly defined adequate accounting for drop-outs and cross-overs with numbers sufficiently low to have minimal potential for bias relevant baseline characteristics are presented and substantially equivalent among treatment groups or there is appropriate statistical adjustment for differences.
B = Probably effective, ineffective, or harmful for the given condition in the specified population.	Level B rating requires at least one convincing class II study or at least three consistent class III studies.	Class II: Prospective matched group cohort study in a representative population with masked outcome assessment that meets a–d above or a RCT in a representative population that lacks one criteria a–d.
C = Possibly effective, ineffective, or harmful for the given condition in the specified population.	Level C rating requires at least two convincing and consistent class III studies.	Class III: All other controlled trials (including well-defined natural history controls or patients serving as own controls) in a representative population, where outcome assessment is independent of patient treatment.
U = Data inadequate or conflicting. Given current knowledge, treatment is unproven.		Class IV: Evidence from uncontrolled studies, case series, case reports, or expert opinion.

dence; see table for definition of levels of evidence), which has been presented in preliminary form.¹⁶ A small phase II pilot trial¹⁷ studied 10 patients with clinically definite MS (CDMS),¹⁸ six of whom had RRMS and four of whom had SPMS. All patients had had an increase of at least one point on the Disability Status Scale (DSS)¹⁹ in the year preceding study entry. The average DSS score in the group was 6.0 with a range of 3 to 9. Patients received mitoxantrone 12 mg/m² at 3-month intervals over 1 year. After 1 year of treatment, the mean DSS score had decreased to 5.1 (NS) and the number of Gd-enhancing MRI lesions had been reduced from 169 prior to therapy to 10 lesions at 12 months ($p < 0.05$). The study was nonblinded and lacked a control group (Class IV evidence). In 1993, the results of an open-label trial of mitoxantrone in 13 patients with progressive CDMS were reported.²⁰ Patients had to have worsened by one or more Extended Disability Status Scale (EDSS)²¹ point over the previous 18 months (not in the setting of an acute exacerbation). Each patient received a dose of 8 mg/m² every 3 weeks, for a total of seven courses. Following mitoxantrone treatment, only three of the 13 patients had an increase of more than 0.5 point on the EDSS.²⁰ Despite this, however, when the authors compared this group to an historical control group from the

multicenter Canadian Cyclophosphamide and Plasmapheresis Trial,⁷ they concluded that there was no obvious clinical benefit to mitoxantrone therapy. This trial, however, was nonblinded and noncontrolled (Class IV evidence).

In 1994, the results of a randomized, double-blind, placebo-controlled trial of mitoxantrone (8 mg/m² per month for 1 year) in 25 patients with MS (13 of whom were treated with active drug) were reported.²² All patients had RRMS with at least two attacks in the 2 years preceding study entry. The mean EDSS score was 3.7 in the treated group and 3.5 in the placebo group. At 1 year there was a reduction (relative to placebo) in the mean number of exacerbations per patient (–68%; $p = 0.014$) following treatment. There was also a reduction in the number of Gd-enhancing lesions, and a reduction in the percentage of patients with a one-point deterioration on the EDSS scale, but these observations were not significant. This study, however, was quite small and the adequacy of the blinding is not assessed. This latter point is important, at least for the clinical measures, because mitoxantrone imparts a bluish color to the urine and potentially the sclera, which could interfere with the blinding. As a result, this study provides Class II data that mitoxantrone reduces the clinical attack rate in patients with RRMS.

There was no demonstrated effect of treatment on measures of disability in this study although it is underpowered for these outcomes.

In 1997, the results of a randomized, nonblinded, controlled trial of mitoxantrone (20 mg IV/month) and methylprednisolone (1 g IV/month) in 42 patients with active MS (21 of whom were treated with both drugs and 21 of whom received only methylprednisolone) were reported.¹³ The authors acknowledged the impossibility of keeping either the patient or the treating physician blind to the treatment assignment due to the blue coloration of the sclera and urine, the occurrence of other side effects from the mitoxantrone, and the fall in white blood cell counts following therapy. The decision to use nonblinded clinical observers for this trial was made for economic reasons. Patients who entered the trial had either RRMS or SPMS and were required to have either two attacks with clinical sequelae or a two-point progression on the EDSS scale within the 12 months prior to entry. In addition, subjects were required to have one active lesion on MRI during the 2 months of baseline observation (three scans) in order to be eligible. Baseline mean EDSS scores were 4.7 in the control group and 4.4 in the mitoxantrone group. The primary endpoint for the trial was the percentage of patients developing Gd-enhancing lesions on each of serial monthly MRI scans. At 6 months, the percentage of patients in the mitoxantrone group without enhancing lesions was significantly greater than the comparable percentage in the control group (+59.2%; $p < 0.001$). The clinical relapse rate was also reduced (-77%; $p < 0.01$), as was the confirmed one-point EDSS progression rate (-83%; $p < 0.01$). The significance of this latter observation was done using a χ^2 analysis based on the number of patients who were worse, no different, or better in each treatment arm. The p value of 0.01 was due mostly to a 400% increase in the number of patients with clinical improvement (more than one point on the EDSS scale) in the mitoxantrone-treated group compared to the control group (see reference 22 for a discussion of problems with such an outcome). Potential concerns about this trial are the limited number of subjects studied, the lack of blinding for clinical outcomes, and the fact that the benefit to treatment was due mostly to a marked improvement in the treated arm. This latter observation is of concern because the EDSS is a subjective clinical score, and one would not anticipate immunosuppressive therapy to radically reverse existing disability. As a result, this study provides Class III data in favor of clinical efficacy. The data in favor of an effect of mitoxantrone on MRI lesion activity, by contrast, are Class II because the interpreting radiologists were blind to treatment assignment.

In 1997, the results of a multicenter, randomized, single-blind, placebo-controlled trial of mitoxantrone (8 mg/m² per month for 1 year) in 51 patients with RRMS who had at least two exacerbations in the prior 2 years were reported.²³ Twenty-seven patients

received active drug. The mean EDSS score at baseline was 3.6 in the mitoxantrone group and 3.5 in the placebo group. After 2 years of observation, there was a reduction in the rate of confirmed one-point EDSS deterioration in the mitoxantrone group compared to placebo (-80%; $p = 0.02$). However, five of the eight patients with confirmed progression in the first year subsequently improved on their EDSS score in the second year, indicating that confirmed progression is often only transient. Also, there was no difference in mean EDSS score between groups at any point during the study. The exacerbation rate was reduced in the treated group compared to controls (-66%; $p = 0.0002$). New lesions on MRI were also reduced in the treatment group compared to placebo-treated patients, although these data were not as strong statistically as the clinical data (-52%; $p < 0.05$). This study provides Class II evidence that mitoxantrone reduces the clinical attack rate in RRMS. The evidence for an effect on the progression of the disease is equivocal.

In 1998, the results of a phase III multicenter, double-blind, controlled trial of mitoxantrone in 188 patients with either RRMS or SPMS (50% of the study population was in each category) were presented in abstract form.^{24,25} The results were presented to the FDA as the basis for drug indication approval,¹¹ which occurred in the fall of 2000 and were recently published.¹² In this trial, patients received mitoxantrone at a dose of either 12 mg/m² (60 patients) or 5 mg/m² (64 patients) every 3 months for a period of 2 years. Patients in the control arm received an infusion of 3 mg of methylene blue (64 patients) on the same schedule. This latter method was undertaken so that patients in all treatment arms would potentially experience blue coloration of their sclera and urine lasting for approximately 3 days and, thus, would remain blinded to treatment assignment. Patients enrolled in the trial were required to have an EDSS score between 3 and 6 and had to have either SPMS or RRMS with residual deficits after relapse. In either case they had to have sustained a deterioration of at least one point on the EDSS scale in the 18 months prior to study entry. The mean EDSS scores in the three treatment arms were high dose (4.45), low dose (4.64), and control (4.69). The range of EDSS scores studied was 3.0 through 6.0 inclusive. The mean EDSS increase for the group during the previous 18 months was 1.57 points.

The main aim of the trial was to evaluate the effect of mitoxantrone on disease progression. The primary outcome was a composite measure of mean EDSS, ambulation index (AI), standardized neurologic status (SNS), time to first attack requiring steroids, and median time to first attack. The outcome on this composite measure was reported to be better in the high-dose arm compared to placebo ($p < 0.0001$). This composite measure, however, is a non-standard outcome measure and several of its component scores, such as the EDSS and the AI, are known

to be highly correlated. As a result, the composite contains redundant information that might distort the findings. These considerations raise concerns about the validity of this measure. More importantly, because the physician evaluating attacks was not blinded, the observations on the primary outcome represent only Class III evidence of efficacy.

Nevertheless, this trial also reported improvements on several of the individual components of the composite score. Thus, the number of patients with deterioration of one point or more on the EDSS scale was reduced in the high-dose arm compared to controls (-64% ; $p = 0.013$). Interestingly, this level of statistical significance was achieved only after a re-analysis of the study data (by Immunex) identified an additional two patients in the placebo arm and another patient in the low-dose arm who had deteriorated to this extent (Immunex Corp., personal communication). There was also a reported improvement in the high-dose group compared to controls on other related outcomes, including the 6-month confirmed one-point EDSS progression rate ($p = 0.045$), the mean 2-year change in the EDSS ($p = 0.0194$), the AI ($p = 0.0306$), and the SNS ($p = 0.0269$). Again, the p values of these last three observations were improved by the data re-analysis (Immunex Corp., personal communication). After 3 years of follow-up (in 138 patients), only SNS change remained significant ($p = 0.0383$), whereas the change in EDSS and AI had reverted to nonsignificance.¹¹ The effect of mitoxantrone on clinical attack rate measures was stronger statistically, although, unlike the EDSS determination, the physician evaluating attacks was not blinded (Class III). Thus, patients treated with mitoxantrone had a reduction in the number of clinical attacks (-67% ; $p = 0.0002$) and the median time to first relapse was significantly prolonged ($p = 0.009$). However, as discussed above, these observations represent only Class III evidence.

The effect of mitoxantrone on measures of MRI outcome generally mirrored the clinical data. The mean change (compared to baseline) in number of Gd-enhancing lesions in the high-dose arm (-2.03) compared to controls (-0.19) was not different ($p = 0.1048$) between groups.^{11,12} Paradoxically, the low-dose arm had the greatest mean change of any treatment arm (-3.27 ; no statistical comparisons provided against either group). By contrast, there was a reduction in the number of T2 lesions ($p = 0.0272$) and the number of patients with new Gd-enhancing lesions ($p = 0.022$) comparing the mean change in the high-dose arm to that in controls. On these measures the low-dose arm was intermediate between the high-dose and control arms. The change in burden of white matter disease (as measured by the change in T2 lesion volume) was not significantly different between the high-dose arm and controls ($p = 0.1228$). In summary, this study provides Class II and III data for an effect of mitoxantrone in reducing the clinical and MRI measures of attack rate in relapsing forms of MS. It may also reduce clinical

disability and MRI measures of disease severity in this patient population, although the statistical evidence is less clear in this regard.

There are some potential concerns about the use of methylene blue in the placebo arm of this trial as if it were an inert compound, because methylene blue is well known to have biologic effects.²⁶⁻²⁸ Moreover, it is also known to be neurotoxic when administered either intraventricularly or intrathecally to humans.²⁹⁻³⁶ Reported complications from these routes of administration include nausea, stupor, headache, weakness or numbness in the arms or legs, pain, facial paresis, optic neuropathy, spinal cord necrosis, and even death.²⁹⁻³⁶ The fact that methylene blue can be neurotoxic in humans complicates the interpretation of the pivotal mitoxantrone trial results, especially in circumstances where 17 to 22% of placebo patients had openings in their blood-brain barrier (BBB) at the time of each methylene blue administration.¹¹

The short-term side effects observed in the two pivotal trials of mitoxantrone were generally mild but common complaints (in more than 25 to 30% of treated patients) included nausea, menstrual disturbances, alopecia, upper respiratory infections, and urinary tract infections. Surprisingly similar, but less frequent, side effects of alopecia (31%), menstrual disorders (26%), nausea (20%), urinary infections (13%), and amenorrhea (3%) were also found in the "placebo" arm of the pivotal trial.^{11,12} By contrast, these same side effects were either not found, or were very much less frequent, in the earlier trial that used methylprednisolone (not methylene blue) in the "placebo" arm.¹³

Conclusion. There is evidence from several Class II and III studies that mitoxantrone reduces clinical attack rate and attack-related MRI outcome measures in patients with relapsing forms of MS. Use of this agent in relapsing MS, however, will have to take into account its potential toxicity. Patients treated with mitoxantrone are at increased risk for cardiac toxicity as manifested by cardiomyopathy, reduced left ventricular ejection fraction, and irreversible congestive heart failure.^{37,38} Recently, an analysis of the clinical data from three combined clinical trials of mitoxantrone (mean cumulative dose = 60.5 mg/m^2) in MS has been reported.³⁹ Although the occurrence of congestive heart failure was low (0.2%) in this study group, an asymptomatic reduction in ejection fraction ($<50\%$) was almost three times less likely (1.8%) at cumulative doses of $<100 \text{ mg/m}^2$ compared to cumulative doses above this. Moreover, in a recently published study (also incorporating data from three separate studies) of 802 patients with MS treated with mitoxantrone in France⁴⁰ (median dose = 70 mg/m^2 ; median follow-up interval = 2 years), 12 patients developed a left ventricular ejection fraction of $<50\%$ and in three of these, the reduction persisted after discontinuation of medication. Because of concerns about such poten-

tial cardiac toxicity, a cumulative dose of mitoxantrone more than 140 mg/m² is not recommended for treatment of MS, although doses of up to 96 mg/m² seem to be safe.³⁷ At a dose of 12 mg/m² administered every 3 months, this limitation (140 mg/m²) translates to a maximum duration of therapy of only 2 to 3 years. Such a therapeutic approach may be inadequate in a disease that will likely require ongoing treatment over many years. Moreover, the optimal way to monitor patients for potential cardiotoxicity (e.g., MUGA scans, echocardiograms) is unknown, as are the risks of long-term cardiac toxicity from short-term treatment. Similarly, whether the limit of 140 mg/m² is safe for all patients or whether there is a bell-shaped curve for individual susceptibility to such toxicity remains to be determined.

Other potential side effects include amenorrhea, which occurred in 43% of the women in the phase III trial^{11,12} and which, in some instances, is permanent. There is also a risk of late malignancy. A recent population-based study of 3,093 women with breast cancer reported a dose-dependent increase in the risk of nonlymphoid acute leukemia in patients treated with mitoxantrone.⁴¹ At cumulative doses of more than 56 mg/m², the standardized incidence ratio for leukemia in women treated with mitoxantrone was 125.8 ($p < 0.0001$). By contrast, chemotherapy without mitoxantrone had a standardized incidence ratio of only 5.4 (not significant). Interpretation of this trial is complicated somewhat by the fact that patients generally received other antineoplastic therapies (including radiation) in both the mitoxantrone and nonmitoxantrone treatment arms. Thus, in the previously cited French study of mitoxantrone in 802 patients with MS, there were two patients who developed acute leukemia.^{40,42} However, there have also been other anecdotal reports in the literature of leukemia developing in patients with MS,⁴³ and it may well be that this association is not as rare as is currently believed by some.

As a result of considerations such as those outlined above, it seems that mitoxantrone should not be used in preference to other immunomodulatory agents in the treatment of patients with relapsing-remitting disease.⁴⁴ Some have suggested, therefore, using mitoxantrone later in the disease course, perhaps to halt disease progression in patients with advanced MS who are deteriorating clinically and where other immunomodulatory treatments have already been tried and failed. No strong recommendation regarding this view can be made, however, because this is not the patient population that has been studied to date. Indeed, the patients in the mitoxantrone trials have had considerably less advanced disease than the patients studied in other trials in SPMS.⁴⁵⁻⁴⁷ Thus, the mean EDSS was only 4.45 in the phase III mitoxantrone trial and the EDSS range did not include patients with an EDSS score of more than 6.0.^{11,12} Moreover, 50% of the patients studied were still in the relapsing-remitting phase of their illness.¹² By contrast, the other SPMS

trials studied patients with a mean EDSS of over 5 and included patients up to an EDSS of 6.5. Also, the patients in the phase III mitoxantrone trial^{11,12} had a disease duration that was considerably shorter than in the other SPMS trials.⁴⁵⁻⁴⁷ By contrast, in the rate of disease progression (measured in EDSS points accumulated in the previous 18 to 24 months), this trial was comparable to other trials in SPMS.⁴⁵ This measure of progression, however, does not account for the widely recognized nonlinearity of the EDSS scale.

Importantly, the failure of the large North American IFN β -1b SPMS trial to replicate the apparently robust therapeutic effects found in European IFN β -1b SPMS trial indicates that physicians need to be cautious about accepting too readily the results from any single trial in the treatment of progressive MS. Because of the modest clinical benefits on disease progression reported in the pivotal phase III mitoxantrone trial, this result should be replicated in another (and hopefully much larger) clinical trial before mitoxantrone can be recommended widely for the treatment of patients with MS.

Practice recommendations

1. On the basis of evidence from a single Class I study and a few Class II or III studies, it appears that mitoxantrone may have a beneficial effect on disease progression in patients with MS whose clinical condition is deteriorating (Type B recommendation). In general, however, this agent is of limited use and of potentially great toxicity. Therefore, it should be reserved for patients with rapidly advancing disease who have failed other therapies.
2. On the basis of several consistent Class II and III studies, mitoxantrone probably reduces the clinical attack rate and reduces attack-related MRI outcomes in patients with relapsing MS (Type B recommendation). The potential toxicity of mitoxantrone, however, considerably limits its use in patients with relapsing forms of MS.
3. Because of the potential toxicity of mitoxantrone, it should be administered under the supervision of a physician experienced in the use of cytotoxic chemotherapeutic agents (Type A Recommendation). In addition, patients being treated with mitoxantrone should be monitored routinely for cardiac, liver, and kidney function abnormalities (Type A Recommendation).

Recommendations for future research

1. A large, multicenter trial of mitoxantrone is essential to confirm the apparent benefit in the treatment of SPMS. This need is especially acute for patients who fail immunomodulatory therapy or in whom combination therapy with immunomodulatory agents is being contemplated. Also, because of potential difficulties with the use of

methylene blue as a placebo, other means of observer blinding should be employed and both clinical and MRI outcomes need to be assessed.

2. Mitoxantrone treatment for 2 to 3 years must be demonstrated to impact favorably long-term outcome in order to justify its potential risk to patients.
3. It would be of value to measure the relative effectiveness of mitoxantrone compared to other immunosuppressive agents (e.g., booster cyclophosphamide treatments⁴⁸) with similar biologic effects, but that can be administered for prolonged periods without the cardiac toxicity that limits prolonged use of mitoxantrone.
4. It would be useful to explore the possible benefit of a very brief course of mitoxantrone in patients who are deteriorating rapidly despite optimal disease modifying therapy and thereby potentially halt the clinical decline. In this way, the cumulative dose of mitoxantrone could be limited and the same therapeutic strategy could be employed subsequently if the patient deteriorated again. The clinical utility of such a therapeutic approach should be studied.
5. Strategies employing potential cardioprotective agents, to be used in conjunction with mitoxantrone, should be explored. Such strategies might allow mitoxantrone to be used over a longer period of time. The long-term cardiac toxicity of short-term treatment also needs to be explored, as does the possibility that there may be individual variation in the susceptibility to such toxicity.
6. Different dosing regimens of mitoxantrone need to be explored in order to possibly prolong the duration of potential therapy.

Disclaimer. This statement is provided as an educational service of the American Academy of Neurology. It is based on an assessment of current scientific and clinical information. It is not intended to include all possible proper methods of care for a particular neurologic problem or all legitimate criteria for choosing to use a specific procedure. Neither is it intended to exclude any reasonable alternative methodologies. The AAN recognizes that specific care decisions are the prerogative of the patient and the physician caring for the patient, based on all of the circumstances involved.

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Appendix: Members of the Therapeutics and Technology Assessment Subcommittee

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References

1. Crespi MD, Ivanier SE, Genovese J, Baldi A. Mitoxantrone affects topoisomerase activities in human breast cancer cells. *Biochem Biophys Res Commun* 1986;136:521–528.
2. Fidler JM, Quinn De Joj S, Smith III FR, Gibbons JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. Non-specific adherent suppressor cell derived from mitoxantrone treated mice. *J Immunol* 1986;136:2747–2754.
3. Fidler JM, Quinn De Joj S, Gibbons JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. Suppression of B lymphocyte function. *J Immunol* 1986;137:727–732.
4. Rosenberg LS, Carvlin MJ, Krugh TR. The antitumor agent mitoxantrone binds cooperatively to DNA: evidence for heterogeneity in DNA conformation. *Biochemistry* 1986;25:1002–1008.
5. Silberberg DH. Azathioprine in multiple sclerosis: the cons. *Neurology* 1988;38(suppl):24–27.
6. The MS Study Group. Efficacy and toxicity of cyclosporin in chronic progressive multiple sclerosis: a randomized, double-blinded, placebo-controlled clinical trial. *Ann Neurol* 1990;27:591–605.
7. Canadian Cooperative MS Study Group. The Canadian cooperative trial of cyclophosphamide and plasma exchange in progressive multiple sclerosis. *Lancet* 1991;337:441–446.
8. Goodin DS. The use of immunosuppressive agents in the treatment of multiple sclerosis: a critical review. *Neurology* 1991;41:980–985.
9. Noseworthy JH, O'Brien P, Erickson BJ, et al. The Mayo Clinic-Canadian cooperative trial of sulfasalazine in active multiple sclerosis. *Neurology* 1998;51:1342–1352.
10. Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI Study Group. *Neurology* 2000;54:1145–1155.
11. Immunex Corp. Briefing document on mitoxantrone (Novantrone) for treatment of multiple sclerosis: on file with the FDA. Available at: www.fda.gov/ohrtms/dockets/ac/00/backgrd/3582b1k.pdf
12. Hartung HP, Gonsette R, König N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002;360:2018–2025.
13. Edan G, Miller D, Clanet M, et al. 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* 1997;62:112–118.
14. Ridge SC, Sloboda AE, McReynolds RA, et al. Suppression of experimental allergic encephalomyelitis with mitoxantrone. *Clin Immunol Immunopathol* 1985;35:35–42.
15. Lublin FD, Lavasa M, Viti C, Knobler RL. Suppression of acute and relapsing experimental allergic encephalomyelitis with mitoxantrone. *Clin Immunol Immunopathol* 1987;45:122–128.
16. Gonsette RE, Demonty L. Immunosuppression with mitoxantrone in multiple sclerosis: a pilot study for 2 years in 22 patients. *Neurology* 1990;40(suppl 1):261.
17. Mauch E, Kornhuber HH, Krapf H, et al. Treatment of multiple sclerosis with mitoxantrone. *Eur Arch Psychiatry Clin Neurosci* 1992;242:96–102.
18. Poser CM, Paty DW, Scheinberg L, et al. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. *Ann Neurol* 1983;13:227–231.
19. Kurtzke JF. Further notes on disability evaluations in multiple sclerosis with scale modifications. *Neurology* 1965;15:654–661.
20. Noseworthy JH, Hopkins MB, Vandervoort MK, et al. An open-trial evaluation of mitoxantrone in the treatment of progressive MS. *Neurology* 1993;43:1401–1406.
21. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983;33:1444–1452.
22. Bastianello S, Pozzilli C, D'Andrea F, et al. A controlled trial of mitoxantrone in multiple sclerosis: serial MRI evaluation at one year. *Can J Neurol Sci* 1994;21:266–270.
23. Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing-remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997;244:153–159.
24. Hartung HP, Gonsette R, et al. Mitoxantrone in progressive multiple sclerosis (MS): a placebo-controlled randomized, observer-blind European phase III multicenter study—clinical results. *Mult Scler* 1998;4:325.
25. Krapf H, Morrissey SP, Zenker O, et al. Mitoxantrone in progressive multiple sclerosis (MS): a placebo-controlled randomized, observer-blind European phase III multicenter study—MRI results. *Mult Scler* 1998;4:380.
26. Kupfer A, Aeschlimann C, Cerney T. Methylene blue and the neurotoxic mechanisms of ifosfamide encephalopathy. *Eur J Clin Pharmacol* 1996;50:249–252.
27. Pelgrims J, Vos F, Van den Brande J, et al. Methylene blue in the treatment and prevention of ifosfamide-induced encephalopathy: report of 12 cases and a review of the literature. *Br J Cancer* 2000;82:291–294.
28. Martindale W. *Martindale: the extra pharmacopoeia*, 31st edition. London: Royal Pharmaceutical Society, 1996;985.

29. Walker AE. Spontaneous ventricular rhinorrhea and otorrhea. *J Neuro-pathol Exp Neurol* 1949;8:171–183.
30. Arieff AJ, Pyzik SW. Quadriplegia after intrathecal injection of methylene blue. *JAMA* 1960;173:794–797.
31. Evans JP, Keegan HR. Danger in the use of intrathecal methylene blue. *JAMA* 1960;174:856–859.
32. Wolman L. The neuropathological effects resulting from the intrathecal injection of chemical substances. *Paraplegia* 1966;4:97–115.
33. Strik F. A transient caudal syndrome following intrathecal injection of phenol red. *Psychiatry Neurol Neurochir* 1967;70:135–140.
34. Schultz P, Schwartz GA. Radiculomyelopathy following intrathecal instillation of methylene blue. *Arch Neurol* 1970;22:240–244.
35. Gross SW. Letter to the editor. *Neuroradiology* 1974;7:117.
36. Sharr MM, Weller RO, Brice JG. Spinal cord necrosis after intrathecal injection of methylene blue. *J Neurol Neurosurg Psychiatry* 1978;41:384–386.
37. DeCastro S, Cartoni D, Millefiorni E, et al. Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *J Clin Pharmacol* 1995;35:627–632.
38. Strotmann JM, Spindler M, Weibach FX, et al. Myocardial function in patients with multiple sclerosis treated with low-dose mitoxantrone. *Am J Cardiol* 2002;89:1222–1225.
39. Ghalie RG, Edan G, Laurent BS, et al. Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 2002;59:909–913.
40. Edan G, Brochet B, Brassat D, et al. Safety profile of mitoxantrone in a cohort of 802 multiple sclerosis patients. *Neurology* 2002;58:A168.
41. Chaplain G, Milan C, Sigro C, et al. Increased risk of acute leukemia after chemotherapy for breast cancer: a population-based study. *J Clin Oncol* 2000;18:2836–2842.
42. Brassat D, Recher C, Waubant E, et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. *Neurology* 2002;59:954–955.
43. Vicari AM, Ciceri F, Folli F, et al. Acute promyelocytic leukemia following mitoxantrone as a single agent for the treatment of multiple sclerosis. *Leukemia* 1998;12:441–442.
44. Goodin DS, Frohman EM, Garmany GP, et al. Disease modifying therapies in multiple sclerosis. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology and the MS Council for Clinical Practice Guidelines. *Neurology* 2002;57:2185–2190.
45. European Study Group on Interferon β -1b in Secondary Progressive MS. Placebo-controlled multicentre randomised trial of interferon β -1b in treatment of secondary progressive multiple sclerosis. *Lancet* 1998;352:1491–1497.
46. Goodkin DE, North American Study Group. Interferon beta-1b in secondary progressive MS: clinical and MRI results of a 3-year randomized controlled trial. Abstract LBN.004. Proceedings of the annual meeting of the American Academy of Neurology; 2000; San Diego, CA.
47. SPECTRIMS Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology* 2001;56:1496–1504.
48. Weiner HL, Mackin GA, Orav EJ, et al. Intermittent cyclophosphamide pulse therapy in progressive multiple sclerosis: final report of the Northeast Cooperative Multiple Sclerosis Treatment Group. *Neurology* 1993;43:910–918.

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