

REPORT NUMBER 3

**SHOULD THE MUHC USE MITOXANTRONE IN
THE TREATMENT OF MULTIPLE SCLEROSIS?**

A Technology Assessment

By

**The Technology Assessment Unit (TAU)
of the McGill University Health Centre
(MUHC)**

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Invitation. This document was designed to assist decision-making in the McGill University Health Centre. Others are welcome to make use of it, preferably with acknowledgment. More important, to assist us in making our own evaluation, it would be *deeply appreciated* if potential users could inform us whether it has influenced policy decisions in any way, and even if it has not, whether it has been helpful in informing decision makers.

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ABBREVIATIONS

AI:	Ambulation Index
ATC:	Anatomical Therapeutic Chemical Classification system
CHF:	Congestive heart failure
FDA:	US Food and Drug Administration
ECG:	Electrocardiogram
EDSS:	Expanded Disability Status Scale
i.v.:	Intra-venous
LVEF:	Left ventricular ejection fraction
MNH:	Montreal Neurological Hospital
MP:	Methylprednisolone
MRI:	Magnetic resonance imaging
MS:	Multiple sclerosis
MUHC:	McGill University Health Centre
MX:	Mitoxantrone
NS:	Non-statistically significant
PPMS:	Primary progressive multiple sclerosis
PRMS:	Progressive relapsing multiple sclerosis
QALY:	Quality-adjusted life year
RRMS:	Relapsing-remitting multiple sclerosis
s.c.:	Sub-cutaneous
SNS:	Standardized Neurological Scale
SPMS:	Secondary progressive multiple sclerosis

SUMMARY

This report reviews the evidence of the value of mitoxantrone in the treatment of multiple sclerosis, estimates the direct costs to the MUHC of such treatment, and formulates recommendations concerning its use in the MUHC for the treatment of the relapsing-remitting, and secondary progressive forms of the disease.

Mitoxantrone is currently approved by the U S Food and Drug Administration for the control of multiple sclerosis, but application has not yet been made for its approval in Canada.

Evidence of its benefit is based on three randomized clinical studies. These are consistent in providing evidence of a beneficial effect of mitoxantrone on the progression of MS. Over the short term there is a reduction in attack rate, a reduction in the rate of development of new cerebral lesions detected by MRI, and a reduction in the number of patients who experience deterioration in function. However, the amount by which progression of disability can be retarded is not yet clear. In the biggest study (188 subjects) with the longest follow-up (3 years), although fewer treated individuals experienced functional deterioration, there was no significant difference between the average change in disability levels from baseline, between the treated and control groups. It is still too early to know whether those benefits that are experienced during treatment will persist.

Compared to other forms of chemotherapy, mitoxantrone has relatively few side effects. Patients receiving high doses are at risk of cardiomyopathy, but at the dosage levels envisaged in the current treatment protocol for multiple sclerosis treatment this risk is low. There is concern that mitoxantrone use may increase the risk of developing malignancies.

A full course of treatment lasts approximately two years. The average direct *net* cost per patient to the MUHC would be approximately \$5,000. If unrestricted, the number

entering treatment might be 40 per year at an estimated *net* direct cost to the institution of approximately \$200,000

Conclusion and Recommendation

- **There is relatively good evidence that treatment with mitoxantrone can be expected to reduce the relapse rate and the rate of clinical deterioration, as well as MRI evidence of diminished CNS activity, at least during the course of treatment.**
- **The clinical benefits to be expected, although not very substantial and not yet shown to be permanent, are still sufficient to justify offering patients with very active forms of MS, similar to those in reported studies, the possibility of treatment.**
- **In view of the above, and in light of the present budget situation, it is recommended that a programme limited to 20 new enrollments per year should be approved at this time. This decision should be reviewed in one year in light of the experience accumulated, and of any new evidence concerning benefits and side effects of mitoxantrone and of competing treatments.**

Should the MUHC use Mitoxantrone in the Treatment of Multiple Sclerosis?

FOREWORD

On May 16, 2002, the Technology Assessment Unit (TAU) of the McGill University Health Centre (MUHC) received a request from the Associate Director General of the Montreal Neurological Hospital (MNH), Mr. James Gates, to provide some guidance on the use of mitoxantrone (MX) to treat chronic relapsing cases of multiple sclerosis at the McGill University Health Centre (MUHC). It should be noted that MX has to be administered intravenously to ambulatory patients while they are in-hospital for a typical duration of one day. As a consequence, the costs incurred by offering MX therapy to MS patients are assumed by the hospital. The TAU agreed to proceed to a formal evaluation at the June 18, 2002 Committee Meeting.

METHOD

Two specific databases were selected to identify randomized clinical trials of mitoxantrone in multiple sclerosis: 1- MEDLINE and 2- Cochrane Library. The following were used as keywords in the search: “mitoxantrone” combined with “randomized” and “multiple sclerosis”. The Cochrane Library contains systematic, up-to-date reviews of randomized controlled trials (RCTs). The library was used to search for RCTs that may not have been identified through the MEDLINE search. A thorough manual screening of bibliographies completed the identification of relevant studies.

INTRODUCTION

This report brings together the available evidence on the usefulness of mitoxantrone (Novantrone® and generics) in the treatment of multiple sclerosis (MS), and formulates recommendations concerning its potential use in the MUHC for the treatment of chronic relapsing MS.

MS is a chronic autoimmune disease of the central nervous system that, in its various stages, affects over one third of a million people in the United States [1] and more than 2.5 million throughout the world [2]. Four different clinical courses of MS have been defined [3]:

- Relapsing-remitting multiple sclerosis (RRMS) is the commonest form of the disease(80-85%). It is characterized by one or more attacks, followed by complete or partial recovery [2,4].
- Secondary progressive multiple sclerosis (SPMS) eventually develops in the majority of cases. It is characterized by slowly increasing disability with or without additional relapses.
- Primary progressive multiple sclerosis (PPMS), (approximately 10 %) is characterized by progressive clinical deterioration from the onset.
- Progressive relapsing multiple sclerosis (PRMS), (approximately 5%) is characterized by progressive disability accompanied by superimposed relapses.

The majority of patients with MS will eventually develop active progressive forms of the disease that significantly impair function. Although some drugs have been shown to reduce the frequency and severity of relapses or to slow disease progression (Appendix 1), there is currently no established treatment to halt the progression of MS.

EVIDENCE FOR THE USE OF MITOXANTRONE IN MULTIPLE SCLEROSIS

Mitoxantrone (Novantrone®, Wyeth-Ayerst; Generic, Faulding) is an immunosuppressant and antineoplastic agent. Although it is not currently approved in Canada for the treatment of MS (the manufacturer has not sought approval), the United States Food & Drug Administration (FDA) has approved MX for reducing neurological disability and/or the frequency of clinical relapses in patients with secondary progressive MS (SPMS), progressive relapsing MS (PRMS), or worsening relapsing-remitting MS (RRMS)[5].

Prior to its approval for MS in the United States, MX was exclusively used to treat certain forms of cancer. It is often used in combination with corticosteroids to treat pain in patients with advanced hormone-refractory prostate cancer and for initial therapy of acute nonlymphocytic leukemia. In people with MS, MX acts by suppressing the activity of inflammatory cells that are thought to lead the attack on the myelin sheath.

MX is approved in Canada for chemotherapy in patients with carcinoma of the breast, including locally advanced and metastatic cancer. MX is also indicated for relapsed adult leukemia, lymphoma patients and patients with hepatoma. In combination with other drugs, MX is also indicated in the initial therapy of acute nonlymphocytic leukemia in adults [6].

Efficacy in multiple sclerosis

Methodological issues. MS studies have used several measurement tools to assess efficacy endpoints. The most common tool to assess disease progression and physical disability is the Expanded Disability Status Scale (EDSS) [7]. EDSS scores range from zero (normal) to 10 (death from MS) in 0.5 step intervals. A score of 6 on the EDSS for instance, indicates inability to walk without an aid. The EDSS does not consider cognitive dysfunction and pain. In a study assessing inter-rater reliability of the EDSS, it was shown that at least 1.0 point on the EDSS is needed to be confident of an important

change in the degree of disability or response to treatment in this disease [8]. Although still used both in the clinical and research settings, disease progression based on the EDSS has been criticized for its inadequate precision in defining the degree of impairment in some functional categories of the scale, and considerable inter-rater variability [8,9].

Other clinical measures used in MS randomized trials (relapse rate, time to progression) are only weakly predictive of the long-term clinical outcomes [4]. While important, neither the rate nor the severity of relapses should be the single outcome to be assessed in MS studies. Indeed, failure of a remission to be complete may be more important than the number and frequency of exacerbations [10].

Disease progression is also commonly evaluated by magnetic resonance imaging (MRI). While there clearly is a relationship between MRI changes and disease progression, the relationship is not sufficiently precise to allow MRI changes to be used as a surrogate for burden of disease or to predict an individual patient's disability [4,10-13]. Because of the different techniques used for MRI evaluation in different studies, comparisons across studies are very difficult.

Current evidence for the use of mitoxantrone in MS

Three randomized clinical studies of MX in multiple sclerosis have been reported (Appendix 2). A study by Bastianello et al. [14] was not included in our review since it reports only interim results from the full study by Millefiorini et al [15].

Millefiorini et al. [15] conducted a randomized, placebo-controlled, multi-center trial involving 51 relapsing-remitting (RR) cases of MS, designed to determine the clinical efficacy of MX 8mg/m² i.v. (n=27) against placebo (n=24) over 2 years. (Assuming an average body surface area of 1.7m² this would be a total dose of 163 mg). Disease progression was evaluated using the Expanded Disability Status Scale (EDSS)

assessed at the beginning of the study and at 12 and 24 months by blinded neurologists. Exacerbations were defined as the appearance of a new symptom or worsening of an old symptom attributable to MS, accompanied by a documented new objective neurological abnormality, lasting more than 48 hours, and preceded by a period of stability or improvement for at least 30 days. Exacerbations were identified and recorded by the unmasked treating physicians. In addition, magnetic resonance imaging (MRI) scans were performed on 42 patients at 0, 12, and 24 months and analyzed by neuro-radiologists blind to treatment received.

Clinical progression. (Blinded). The number of patients with clinical progression of the disease at two years, as indicated by a one-point increase in the EDSS, assessed blinded, was significantly smaller in the MX group (2/27, 7%) compared to placebo (9/24, 37%); $p=0.02$, representing a 30% difference between the two groups (95% CI for the difference= 8%-52%). Significant differences in the average change in EDSS scores between the groups were not observed over the 2-year period (placebo: 0.7 vs. MX: -0.1; $p=NS$), although the lack of significance may have been due to the small sample size.

Exacerbations. (Unblinded). There was a statistically significant difference in the number of exacerbations experienced by patients receiving MX compared with placebo (average, 0.89 vs. 2.62; $p=0.0002$), and in the number of exacerbation-free patients (63% vs. 21%; $p=0.006$) at two years.

MRI.Changes. (Blinded). Among the sub-group of 42 patients who had MRI studies, the median number of new lesions was lower in the MX group compared to placebo (2 vs. 5, $p=0.05$). The number of enlarging lesions was similar (average, 4.3 in both groups).

Comment: This study demonstrated that MX was effective in reducing the frequency of exacerbations, the incidence of new lesions detected by MRI, and evidence of clinical progression in 30 % of the subjects treated, but the overall numbers involved in the study were small. Neither the number who benefited nor the extent of the clinical benefit

were sufficiently large to cause a statistically significant difference in the average EDSS score. (This is not surprising in view of the low event rate. Even in the control group only 9 out of 24 subjects showed progression of disability as defined in the relatively short two year follow up). This study is considered by the American Academy of Neurology to provide Class II evidence in favour of reducing the clinical attack rate in RRMS, while the evidence for an effect on disease progression is considered equivocal [16]. It should also be noted that the attack rates were evaluated unblinded, raising the possibility of both performance and detection biases favoring the treatment group, and the means by which 42 cases were selected for MRI studies is not stated, raising the possibility of selection bias.

Edan et al [17]. These authors conducted a randomized controlled trial of the efficacy of MX as an add-on therapy for the treatment of 42 patients identified as having very active MS, in categories RR and SP. Patients were randomized into two groups, one receiving MX 20 mg i.v. and methylprednisolone (MP) 1 g. i.v. (n=21), and the other receiving the same dose of MP only (n=21), monthly for 6 months. (Assuming an average body surface area of 1.7 m², the average total dose would have been 70 mg / m²).

Five of the subjects in the steroid-only group dropped out of the study due to severe exacerbations as compared with no patients in the combined treatment group.

MRI Changes (Blinded). The primary endpoint was the proportion of patients developing new enhancing lesions as visualized by MRI, assessed blindly every month. At six months patients taking the combination MX-MP had significantly fewer new enhancing lesions than those in the MP-only group (90% vs. 31%; p<0.001). In addition the total number of new enhancing lesions was lower in the MX-MP group compared to placebo (1.1 vs. 5.5; p<0.05).

Clinical progression, relapses, (Unblinded). Secondary endpoints also showed benefit of treatment. The average EDSS score was improved by slightly more than 1 point in

patients taking MX, assessed at 6 months after commencing treatment (Average, -1.1 vs. -0.1; $p < 0.05$). The total number of relapses observed was also lower in the MX group (7 vs. 31; $p < 0.01$).

Comment: Unlike the previous study, this group of patients suffered from an extremely active and rapidly deteriorating form of MS. Both the primary outcome, frequency of new lesions on MRI interpreted blinded, and the secondary outcomes, clinical deterioration and exacerbation rate, interpreted unblinded, showed significant benefit of treatment. However, the number of subjects is again small, and the clinical outcomes were assessed unblinded.

Hartung et al.[18]. In this phase III, European, multi-center, randomized trial the efficacy of two different dosages of MX were compared against placebo. The study included 194 patients who had either RRMS or SPMS. Patients were randomized to receive MX 5 mg/m² (n=64), MX 12 mg/m² (n=60), or a placebo (n=64). The medications were given intravenously, once every 3 months for a period of 2 years. (Assuming an average body surface area of 1.7m² this would constitute a total MX dose of 68 mg and 163 mg). Relapses were treated for five days with MP i.v. 500 mg/day.

Blinded observers determined EDSS, Ambulation Index (AI) and Standardized Neurological Status (SNS), while relapses were determined unblinded, using a predetermined definition, the “occurrence of a new episode of neurological symptoms or deficits that last at least 24 hours in the absence of fever or other precipitants of a pseudo-attack”. A subset of 110 patients with "similar" demographics and clinical features to the main population, completed annual unenhanced and gadolinium-enhanced MRI scans of the brain which were read by two experienced readers, masked to treatment assignment. Cardiac monitoring at 12, 24 and 36 months included electrocardiograms and estimates of left ventricular ejection fraction determined by echocardiography or radionuclide scan. The primary endpoint was a composite measure including all three functional scales, EDSS, AI and SNS (all interpreted

blinded), and two relapse measures (the number of treated relapses and time to first treated relapse (interpreted unblinded)).

Composite index. For the primary endpoint, and in the univariate analyses of individual outcomes, patients on MX 12 mg/m² had significant improvement from baseline to the end of the second year as compared with the placebo group. Treatment effects for the 5mg/m² recipients were intermediate. Average outcomes (blinded): EDSS (-0.13 vs. 0.23; p=0.0194), AI (0.30 vs. 0.77; p=0.0306), and SNS scores (-1.07 vs. 0.77; p=0.0269). Unblinded outcomes: the number of treated relapses (24.1 vs. 76.8; p=0.0002), and the time to first relapse (p=0.0004).

Of 73% of patients who completed an additional clinical evaluation at 36 months, 16% compared to 42% deteriorated by at least one point on the EDSS scale, in the MX 12 mg/m² group and the placebo group, respectively. However, there was no significant difference in the change in EDSS scores between the two groups over a three-year period, which again, could be a consequence of the small sample size.

MRI Changes. (Blinded). Significantly fewer patients receiving 12mg/m² MX demonstrated new enhancing lesions on MRI at 24 months compared to placebo (0% vs. 15.6%. p= 0.02), and the mean increase in T2-weighted lesions was less (MX 0.29 vs. placebo 1.94, p=0.03)

Comment: This study found statistically significant evidence of benefit reflected in clinical indices, frequency of attacks, and MRI changes, associated with MX. However, the extent of benefit was not large enough to cause a significant difference in the change in EDSS scale between treated and untreated subjects at two years, or in the extended three-year follow-up cohort.

SAFETY

General safety. Compared to other forms of chemotherapy, MX is relatively easy to use and has minimal side effects and an excellent safety profile at the appropriate dose [6]. The majority of side effects are mild in nature. Company reported safety data based on 989 cancer patients (dosage not specified), suggest a relatively low risk of serious side effects, permitting treatment of patients on an out-patient basis [6]. The most common side effects were nausea and/or vomiting (3.5% severe or very severe with MX), stomatitis/mucositis (0.3% severe or very severe) and alopecia (0.9% severe or very severe; 15% overall). Serious local reactions have also been rarely reported at the infusion site. In leukemia patients, receiving a single course of 12 mg/m² i.v. daily for five days, resulting in a total dose (60 mg/m²) that is much lower but much more intense than that under consideration for MS, the following adverse effects were observed: moderate or severe jaundice or hepatitis (8%), moderate nausea or vomiting (8%), moderate or severe stomatitis/mucositis (9-29%), diarrhea (9-13%), and moderate to severe alopecia (11%) [6]. Fatigue might also be experienced in several patients during 2-3 days after the infusion [19].

Cardiotoxicity. Patients treated with MX are at increased risk of toxic effects as manifested by cardiomyopathy, reduced LVEF, and irreversible CHF [6]. Following earlier animal [22] and human studies [21,23,24] of MX indicating some evidence of cardiac toxicity, de Castro et al. [25] specifically evaluated the cardiac toxicity of MX 96 mg/m² (cumulative dose) against placebo in 20 patients with RRMS. No clinically significant difference in ECG or Doppler results were observed between the two groups with this selected dosage after one year [25]. None of the three efficacy trials of MX in MS at a cumulative dose of 70-96 mg/m² revealed symptomatic cardiotoxicity [15,17,18].

However, an analysis of 1211 cancer patients in whom the total dose of MX could be clearly defined, heart failure developed at approximately the following rates: 80mg/m², 2%. 140 mg/m², 5%. 180 mg/m², 14%. [20]. The authors believe that the cardiac risk of

MX is low when given to patients with no previous cardiotoxic therapies or pre-existing heart disease and at a cumulative dose lower than 160mg/m² [20]. In one study the risk was found to be more pronounced in MS therapy than in cancer treatment [19]. There is evidence of a dose relationship in a study in which signs of cardiotoxicity were observed in 1 of 27 MS patients receiving 50-99 mg/m², in 4 of 14 receiving 100-149 mg/m², and in 2 of 4 receiving 150-199 mg/m² [19].

One reviewer concludes that when mitoxantrone is used in cancer therapy, the incidence of CHF is estimated to be 1.3%, and recommends cardiac monitoring when the cumulative dose exceeds 160 mg/m² [19]. The Canadian Pharmacists Association review, CPS 2000 [6], concludes that in investigational trials of intermittent single doses, patients who were administered up to the cumulative dose of 140 mg/m² had a cumulative probability of clinical CHF of 2.6% and an overall cumulative probability rate of moderate or serious decreases in LVEF as determined by ECHO or MUGA scan of 13%. However, the safety threshold may be even lower. In a clinical study of 25 patients with advanced breast cancer [21], 15 patients who received a cumulative dose equal to, or more than 70 mg/m² (median 81, range 70-84) showed a decrease in the nuclear angiographic ejection fraction more than 15%, though no patients developed CHF. In light of such reports, the possibility of cardiac injury must be considered even with the proposed maximum dose of 110mg/m² for MS treatment.

Malignancies. There is concern that MX, like most chemotherapeutic agents, may increase the risk of developing malignancies [26,27]. In a population based study based on a 2 to 16 year follow-up of 3093 women receiving numerous different treatments, including radiotherapy, for breast cancer, there was an excess 4-year cumulative rate of leukemia of 3.9% for patients receiving a cumulative dose of mitoxantrone of 56 mg/m² or higher as part of their therapy [26]. This may be an important consideration in treating MS patients with this agent since these patients are typically younger and have a better long-term survival than cancer patients, and are accordingly at greater risk of developing drug-induced neoplasms.

Contraindications / Precautions

MX is contraindicated in patients who have demonstrated prior hypersensitivity to anthracyclines. Because it produces myelosuppression, MX should also be used with caution in patients in generally poor condition or with pre-existing myelosuppression. Because cases of functional cardiac changes, including CHF and decreases in LVEF have been reported, especially among patients who had prior treatment with anthracyclines, prior mediastinal radiotherapy, or with pre-existing heart disease, LVEF should be carefully monitored in these patients from initiation of therapy. The lifetime cumulative dose should be limited to 140 mg/m^2 (approximately 12 doses over 2-3 years), after which periodic cardiac monitoring should be performed [6].

Due to the risk of myelosuppression associated with the use of MX, blood counts should be evaluated prior to each dose. Immunization is not indicated while being treated with MX and contacts with people with infections should be avoided. MX may also cause birth defect and should be avoided in pregnancy and at time of conception (for both men and women). Also, because MX is excreted in human milk, breast-feeding should be discontinued during treatment. Finally, MX should not be used in patients with severe hepatic dysfunction and poor performance status [6].

COSTS OF TREATMENT

The protocol to be followed in the MS Clinic is outlined in Appendix 3, and the estimated costs of treatment in Appendix 4. The cost of MX to the MUHC is \$207.72 per 20mg. The dosage recommended by the MS clinic at the MUHC for the treatment of SPMS and RRMS is 12 mg/m^2 administered as an i.v. infusion once a month for three months and then every three months up to a lifetime cumulative dose of 110 mg/m^2 . Assuming an average body surface area of 1.7m^2 , each patient should receive on

average about 20 mg per dose. At the MUHC the treatment protocol proposed (Appendix 3) specifies a lifetime maximal cumulative dose of 110 mg/m² (or approximately 190 mg total per patient, or 10 doses). Thus, MX treatment will continue for a maximum period of 2 years.

The principal costs to the MUHC are as follows: Evaluation of patients before treatment, \$931; treatment and follow-up of patients with SPMS \$6,499, and with RRMS \$3,482, (Appendix 4). The mix of cases in the MS Clinic of the Montreal Neurological Hospital is approximately: RRMS 61%, SPMS 32%. Thus, for the same mix of cases, *the average direct cost to the MUHC of evaluating and treating a patient would be \$5,135. (The cost to the Quebec healthcare system would be \$5,869).*

There are other costs related to MX treatment, such as the cost of managing the occasional case of heart failure that might result from treatment. This is too problematic to include in this analysis. There are also costs related to caring for cases in relapse (experiencing exacerbations) that could potentially be avoided by treatment, and these are more predictable. In the period September 2000 to September 2001 approximately 280 MS exacerbations were recorded in the MS Clinic of the Montreal Neurological Hospital. Over the same period, 39 MS patients were admitted for exacerbations (14%), with an average length of stay of 8.6 days. In the study of Hartung et al, the average annual relapse rate was reduced in treated patients by 0.67[17]. Assuming; that the treatment effect is the same as in this study; that the proportion of relapses requiring hospitalization = 14%; that the average length of stay of hospitalized relapses = 8.6 days; and that the average direct cost (without overheads) of hospitalization = \$273 per day (MUHC, Department of Finance, 2002), the potential cost per year that might be avoided by treating 10 patients would be $10 \times 0.14 \times 0.67 \times 8.6 \times \$273 = \$2,202$, or \$220 per patient treated.

Accepting these assumptions, and ignoring any potential costs of treating cardiotoxicity, *the net direct cost to the MUHC would be approximately \$5,135 - \$220 = \$4,915 per patient treated.*

Impact on Budget

At the present time approximately 10 new patients per year are treated for MS using mitoxantrone, at an estimated annual direct cost to the MUHC of approximately \$51,350. Taking count of the potential costs avoided as a result of treatment, the *net* annual direct cost to the MUHC would be \$49,150. If admission to treatment was unrestricted it is estimated that perhaps 40 patients would be admitted to treatment per year, at an annual net direct cost of \$196,600.

Cost-effectiveness

The effectiveness of this intervention consists of a reduction in the rate of progression of disability and a reduction in the number of relapses. Retardation in rate of progression of disability is too small to measure in terms of average EDSS score. Accordingly no attempt will be made to estimate the cost-effectiveness of this intervention. However, if treatment reduces the rate of exacerbations by 0.69 per year [18], the expenditure by the Québec health-care system of approximately \$5,869 would prevent 1.4 “treatable” relapses during the two years of treatment. Each of these would have caused considerable distress and a varying amount of discomfort, and each would have required a course of intravenous solumedrol, administered either at a CLSC or in hospital. It is not known whether the lower relapse rate would persist in subsequent years. With these assumptions, even without taking count of any reduction in disability, relapses can be reduced by treatment at the cost of approximately \$4,192 per relapse prevented.

DISCUSSION

When considering the prioritization of interventions competing for scarce resources, the TAU believes that the following factors should be considered:

- The **quality of the evidence** of any benefit that might result from the intervention. (The quality and quantity of evidence required to support a decision to commit *shared* resources should be greater than that to support a therapeutic decision concerning an *individual* patient).
- The **amount of the net benefit** that would result.
- The **cost of each benefit** achieved, (The cost-effectiveness of the intervention).
- The **affordability** of the intervention. (The amount by which it will impact on the budget of the institution).
- The **opportunity costs** involved. (In the absence of budget surplus, what are the likely items of expenditure that will have to be reduced?)
- The **societal values**, both ethical and social, of the MUHC community. The Committee of TAU endeavors to take such values into consideration, and when necessary to consult the community more widely).

Level of proof. Although the number of randomized controlled studies is small, they are consistent in providing positive evidence of a beneficial effect of mitoxantrone on MS, insofar as there is evidence of a reduction in attack rates, a reduction in CNS changes judged by MRI, and a reduction in the number of patients showing clinical deterioration.

Extent of benefit. The amount by which clinical deterioration can be retarded by treatment is not substantial. Thus, in the 188 subjects followed up for three years in the large European study, although fewer treated individuals experienced functional deterioration, there was no significant difference between the change in the average disability level from baseline in the treated and in control subjects. There is as yet no evidence as to whether any benefits obtained by treatment will be sustained or not.

Cost per benefit achieved (cost-effectiveness). The extent of the benefit achieved in terms of average *improvement of function* is too small to be objectively measured. However, on average approximately 1.4 *exacerbations* per patient will be prevented during the two years of treatment, at a cost of approximately \$5000.

Affordability. The estimated cost of the proposed program to admit 40 MS patients per year to treatment (approximately \$200,000) is relatively modest in relation to the annual budget of close to \$0.5 billion. Nevertheless, the institution is committed to eliminating a substantial deficit and it can be assumed that new money will not be forthcoming to cover this expense.

Opportunity costs. Accordingly, a new expenditure of \$200,000 per year would necessarily diminish present hospital services by the same amount. It is not possible to identify on which particular aspect of the MUHC's function the fresh expenditure would impact. Such a sum would be the equivalent of permanently closing two medical acute care beds.

Conclusion and Recommendation

- **There is relatively good evidence that treatment with mitoxantrone can be expected to reduce the relapse rate and the rate of clinical deterioration, as well as MRI evidence of diminished CNS activity, at least during the course of treatment.**
- **The clinical benefits to be expected, although not very substantial and not yet shown to be permanent, are still sufficient to justify offering patients with very active forms of MS, similar to those in reported studies, the possibility of treatment.**
- **In view of the above, and in light of the present budget situation, it is recommended that a program limited to not more than 20 new enrollments per year should be approved at this time.**
- **This decision should be reviewed in one year in light of the experience accumulated, and of any new evidence concerning benefits and side effects of mitoxantrone and of competing treatments.**

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Appendix 1.

Current therapies for multiple sclerosis

A large body of literature suggests that immunologic therapies provide the greatest benefits [27]. Several immuno-altering drugs have received approval in the U.S. to safely and effectively modify the course of MS. Three preparations of interferon beta (Avonex®, Betaseron® and Rebif®) and glatiramer acetate (Copaxone®) have all shown to reduce the frequency and severity of RRMS (see 2,4,29,30 for reviews), although at the price of considerable toxicity and expense[28,31,32] and only small gains in QALYs [31]. The interferons also showed promises in slowing the course of SPMS, although this is still controversial [4,29]. Interferon beta-1a appears to be one of the leading drugs in the control of MS. It was the first therapy shown to slow the progression of physical disability as well as to decrease the frequency of neurological attacks in patients with relapsing forms of MS. Avonex® (Biogen) is administered once a week as an intra-muscular (IM) injection. Rebif® (Serono), is another form of interferon beta-1a in use outside the U.S. (including Canada and in Europe), administered by the sub-cutaneous (SC) route. Rebif® and Avonex® are essentially the same drug, other than the route of administration. Interferon beta-1b has exhibited both antiviral and immunoregulatory activities. The mechanisms by which Betaseron® (Berlex Laboratories) exerts its actions are not clearly understood. However, it is known that the biologic response-modifying properties of interferon beta-1b are mediated through its interactions with specific cell receptors found on the surface of human cells. Clinical trials (see 31,32 for reviews) have shown interferon beta 1-b to significantly decrease the frequency of attacks by 28% to 33% in the first two years and a trend to slowing the progression of the disease as measured by the EDSS. The cost of therapy, estimated at \$16,685 annually in 1996, and the incidence of side effects (although mild: flu-like symptoms and pain at the site of injection) are high. Betaseron has not been found to limit the progression of disability [34]. Glatiramer acetate or copolymer 1 is the first non-steroidal, non-interferon MS drug therapy available for relapsing-remitting multiple sclerosis. During 2001, 15 European countries approved Copaxone® (Teva Pharmaceuticals). Copaxone® requires daily administration. No direct comparison of these drugs have been made and since they have been studied in different populations, using different dosages and routes of administration, and with different outcome measures, none of them has been identified as being superior to the others [28].

Current treatment for MS also includes steroids, immunoglobulin, plasma exchange and several chemotherapeutic agents. Steroids were until recently the principal medications for MS [2,4,30,35]. Hence, evidence shows that steroids can reduce the duration and severity of attacks in some patients [2,35,36], although they might fail to reduce disability acquired through relapses [2]. Clinical trial data also suggest a role for intravenous (i.v.) immunoglobulin in MS. Although generally safe and well tolerated, immunoglobulin i.v. is an expensive drug, which limits its role on MS despite its beneficial effect on attack rate [4,28-30].

Several chemotherapeutic agents have also been used in the treatment of MS, with varying degrees of success [30,37]. The most common chemotherapies for the

treatment of MS have been methotrexate, azathioprine, cyclophosphamide, cladribine and mitoxantrone. Among the chemotherapeutic studies conducted, mitoxantrone studies have yielded the most data suggesting benefits to patients with MS, although it is very difficult to compare the results of MX studies against those of other drugs. A systematic review of effectiveness and costs of a range of disease modifying drugs for MS including azathioprine, cladribine, cyclophosphamide, i.v. immunoglobulin, methotrexate, and mitoxantrone) was published in 2000 [4,29,38] and updated in 2001 [39]. Twenty-six studies (cost-effectiveness studies being limited to interferon-beta and glatiramer) were included in the updated review, which conclude that current evidence suggests some benefit of these drugs for MS patients, although with a wide range of side effects. The authors also concluded that evidence for the effectiveness of these drugs in MS is problematic because trials are too few and they suffer from major limitations (short follow-up, inadequate blinding, poor description of withdrawals and use different treatment regimens, study populations and treatment outcomes).

A *Technology Report* by the Canadian Coordinating Office for Health Technology Assessment (CCOHTA, 1998) on the comparison of four drug therapies for multiple sclerosis (the interferon beta 1-a Avonex® and Rebif®, the interferon beta 1-b Betaseron® and the Glatiramer acetate Copaxone®) revealed that all four therapies appear to impact on the progression of the disease [12]. However, variations in study endpoints, characteristics of study populations and differences in the doses used, made a formal comparative evaluation of study results difficult. The authors also concluded that glatiramer acetate seems more useful early in the disease and among RRMS patients. There are more side effects from glatiramer, although most are mild. The reduction in exacerbation rates seemed to be similar among the different therapies (approximately 30% reduction). There is also some evidence of a reduction of moderate and severe attacks. The long-term impact (>3 years) of either treatment with interferon beta or glatiramer acetate is unknown. Finally, since the costs of each product are almost identical, the cost for avoiding an acute exacerbation would be similar to that calculated in the CCOHTA evaluation of Betaseron® (direct treatment costs: \$16695/patient/year in 1996; cost per exacerbation episode avoided: \$30,000-\$50,000) [31].

A more recent review by the American Academy of Neurology and the MS Council for Clinical Practice Guidelines [16] examined the clinical utility of several disease-modifying agents, including the anti-inflammatory (glucocorticoids), immunomodulatory (interferon beta-1a, interferon beta-1b and glatiramer), and immunosuppressive treatments (cyclophosphamide, methotrexate, azathioprine, cladribine, cyclosporine, mitoxantrone) that are currently available. The conclusions of this review, along with the rating of the quality of evidence for each of assessed treatment, are summarized in the following Table.

Clinical utility of disease-modifying agents in multiple sclerosis according to the American Academy of Neurology and the MS Council for Clinical Practice Guidelines [16].

Treatment	Population	Outcome	Quality of evidence*
Interferon-beta	RRMS or SPMS w. relapses	Reduces attack rate	Established
	SPMS without relapses	Treatment effectiveness	Inadequate
	MS	Beneficial effect on MRI measures of disease severity and slows sustained disability progression	Probable
Glucocorticoids	Patients w. acute attacks	Short-term benefit on the speed of functional recovery	Established
	Patients w. acute attacks	No long-term functional effect	Probable
Glatiramer acetate	RRMS	Reduces attack rate	Established
	RRMS	Beneficial effect on MRI measures of disease severity and slows sustained disability progression	Probable
Cyclophosphamide	Progressive MS	Not helpful	Inadequate
	Progressive MS	Does not appear to alter the course of disease	Established
Methotrexate	Progressive MS	Younger patients might derive some benefit	Probable
	Progressive MS	Favorably alters disease course	Possible
Azathioprine	MS	Reduces relapse rate	Possible
	MS	Effect on disease progression not demonstrated	Inadequate
Cladribine	Patients with both relapsing and progressive forms of MS	Reduces Gadolinium enhancing lesions	Established
	Patients w. relapsing and progressive forms of MS	Does not alter favorably the course of disease (attack rate or disease progression)	Possible
Cyclosporine	Progressive MS	Provides some therapeutic benefit	Possible
	Progressive MS	Frequent occurrence of side effects (nephrotoxicity) + small magnitude of the beneficial effect makes the risk/benefit ratio unacceptable	Probable
Mitoxantrone	Relapsing forms of MS	Reduces attack rate; potential cardiac toxicity may outweigh the clinical benefits early in the course of disease	Probable
	MS	Beneficial effect on disease progression	Possible
Immunoglobulin i.v.	RRMS	Reduces attack rate; Little benefit with regard to slowing disease progression	Possible
Plasma exchange	Progressive MS	Little or no value	Established
	Progressive MS	May be helpful in treatment of severe, acute episodes of demyelination in previously non-disabled patients	Possible
Sulfalazine	MS	No therapeutic benefit	Probable

Appendix 2.

Randomized controlled trials of mitoxantrone in the treatment of multiple sclerosis.

Study	Objective	Design	Patients	Measures	Exposure	Outcomes	Results
Millefiorini <i>et al.</i> , 1997[15]	To determine the clinical efficacy and toxicity of MX	Placebo-controlled Multicentre (n=8) RCT Follow-up: 2 yrs	N=51 -RRMS -18-45 yrs -EDSS= 2-5 -≥ 2 exacerb. in last 2 yrs	-EDSS @ 0,12,24 mths [BLINDED] -Exacerbations* (throughout the study) [NOT BLINDED] -MRIs @ 0,12,24 months [BLINDED]	-MX 8 mg/m ² i.v. (n=27) -Placebo (n=24) One injection / month for 12 months [Other drugs allowed –treating physician NOT BLINDED; patient BLINDED]	<u>Primary endpoint:</u> -% pts with confirmed progression* <u>Secondary endpoints:</u> -Annual mean no. of exacerbations* and % of exacerbation-free patients -Change in mean disability measured by EDSS from baseline to endpoint -Mean no. new or enlarged lesions* per MRI @ 0,12,24 months	<u>Primary endpoint:</u> -Confirmed progression of the disease significantly reduced in the MX group (7% of pts) after 2 yrs compared to placebo (37%) (p=0.02) <u>Sec. endpoints:</u> -Significantly 1-less exacerbations in the MX group after 2 yrs (0.89 vs. 2.62; p=0.0002) and 2-more exacerbation-free pts (63% vs. 21%; p=0.006) -No statistically significant benefit in terms of mean EDSS progression over 2 yrs (figures not reported) -NS trend towards a reduction in no. new lesions in the MX group vs. placebo (3.5 vs. 7.3) as per MRI sub-group analyses (n=42 pts; p=0.05); no diff. In no. of enlarging lesions (4.3 in both groups)
Edan <i>et al.</i> , 1977 [17]	To evaluate the efficiency of MX in MS	Multicentre (n=5) RCT Follow-up: 6 mths	N=42 -Very active MS (RRMS & SPMS) -18-45 yrs -MS duration <10 yrs -≥ 2 relapses with sequelae in prior year <u>or</u> ≥ 2-point progression on EDSS in prior year -EDSS ≤ 6	-Gd enh. MRIs monthly from mth -2 to study exit [BLINDED] -EDSS monthly from mth -2 to study exit [NOT BLINDED] -Relapses† monthly from mth -2 to study exit [NOT BLINDED]	-MX 20 mg i.v. + MP 1g i.v. (n=21) -MP 1g i.v. (n=21) Once a month for 6 months [Additional courses of MP i.v. 1g/day for 3 days allowed for relapses NOT BLINDED]	<u>Primary endpoint:</u> -% of pts developing new enhancing lesions per MRI <u>Secondary endpoints:</u> -Mean no. of new enhancing lesions per pt per month -No. new T2 lesions (per MRI) from baseline to exit -Monthly clinical outcome as assessed by EDSS	<u>Primary endpoint:</u> -Significantly more pts without new enhancing lesions in the MX group (90.5% vs. 31.3%; p<0.001) after 6 months <u>Secondary endpoints:</u> -Significant month by month decrease in the no. of new enhancing lesions in the MX group in first 6 months (ranged 0.1-2.6 vs. 2.9-12.3 respectively; all p-values stat. signif.)

Study	Objective	Design	Patients	Measures	Exposure	Outcomes	Results
						-No. exacerbations† (per neurological examination)	<p>-Total no. new T2 lesions (per MRI) lower in the MX group (1.1 vs. 5.5; p<0.05)</p> <p>-Significant improvements in change in EDSS at mths 2-6 in MX group with final mean improvement of more than one point (-1.1 vs. -0.1; p<0.05)</p> <p>-Significant reduction in no. relapses (7 vs. 31; p<0.01) up to mth 6</p> <p>-Drop-outs in the steroid alone group (n=5) due to severe exacerbations</p>
Hartung <i>et al.</i> ,1999[18]	To determine the efficacy of MX in the treatment of relapsing progressive or secondary progressive MS	<p>Multicentre (n=17)</p> <p>Placebo-controlled Phase III RCT</p> <p>Follow-up: 3 yrs</p>	<p>N=194</p> <p>-SPMS or RPMS with residual deficits‡</p> <p>-18-55 yrs</p> <p>-Active disease (≥1-pt progression in EDSS in last 18 mths)</p> <p>-EDSS= 3-6</p>	<p>-Neurological examination every 3 months to determine</p> <p>1.EDSS [BLINDED]</p> <p>2.Ambulation Index (AI) [BLINDED]</p> <p>3.SNS [BLINDED]</p> <p>4.No. treated relapse [NOT BLINDED]</p> <p>5.Time to first treated relapse [NOT BLINDED]</p> <p>-MRI in a subset of n=110 pts @ baseline, 12, 24 mths [BLINDED]</p>	<p>-MX 5 mg/m² (n=64)</p> <p>-MX 12 mg/m² (n=60)</p> <p>-Placebo (n=64)</p> <p>Every three mths for 2 yrs</p> <p>[Relapses treated for 5 days with i.v. MP 500 mg/day NOT BLINDED patients BLINDED]</p>	<p><u>Primary endpoint:</u></p> <p>-Multivariate measure of change from baseline to mth 24 combining 3 functional measures (EDSS, AI, SNS§) and two measures of relapse (no. or treated relapses and time to first treated relapse)</p> <p><u>Secondary endpoints:</u></p> <p>-% patients with EDSS progression</p> <p>-Time to confirmed EDSS progression</p> <p>-No. all relapses</p> <p>-Time to first relapse</p> <p>-% pts with no relapse</p> <p>-No. hospitalizations (?)</p> <p>-Pts with new Gd enhancing lesions per MRI</p> <p>-Change in total T2-weighted lesion load per MRI</p>	<p><u>Primary endpoint:</u></p> <p>-Multivariate test statistically significant (data not reported; p<0.0001), which allowed per protocol to test each of the five primary outcomes independently</p> <p>-Statistically significant results were observed for each independent primary endpoint (all p<0.05) (placebo vs. MX12):</p> <p>1-EDSS change: 0.23 vs. -0.13 (p=0.0194)</p> <p>2-AI change: 0.77 vs. 0.30 (p=0.0306)</p> <p>3-SNS change: 0.77 vs. -1.07 (p=0.0269)</p> <p>4-No. Tx relapses: 76.8 vs. 24.1 (p=0.0002)</p> <p>5-Time to 1st Tx relapse (mths): 14.2 vs. NR (???) (p=0.0004)</p> <p><u>Secondary endpoints:</u></p> <p>-Patients with EDSS progression: 22% vs. 8%; p=0.036)</p> <p>-Annual relapse rate after 2 years: 1.0 vs. 0.4 (p=0.0002)</p> <p>- Pts with new Gd enhancing lesions</p>

Study	Objective	Design	Patients	Measures	Exposure	Outcomes	Results
							and 16% vs. 0% at mth 24; p=0.0236) -Change in total T2-weighted lesion load per MRI: 4.28 vs. 0.64 at mth 24; p=0.125) -For all other sec. endpoints, MX 12 did better -Lost to F/U / withdrawals: n=6 before 1 st assessment and n=39 before end of study

* Progression measured by an increase of at least one point EDSS; Exacerbation defined as “the appearance of a new symptom or worsening of an old symptom, attributable to MS, accompanied by a documented new neurological abnormality, lasting more than 48 h and preceded by stability or improvement for at least 30 days”; New lesions defined as “lesions that were not present on T2-weighted MRI performed 1 year previously”; Enlarging lesions defined as “a lesion with a change exceeding more than 33% (1/3) when compared with the MRI performed 1 year before”[15].

† Relapses (or exacerbations) “documented by neurological examination, marked by the occurrence of symptoms of neurological dysfunction lasting more than 48 hours and preceded by stability or improvement for at least 30 days [17].

‡ Remitting progressive MS patients are those who have relapsing remitting disease with a residual deficit [18].

Abbreviations: AI= Ambulation Index; EDSS= Expanded Disability Status Scale; MP= Methylprednisolone; MX=Mitoxantrone; SNS=Standardized Neurological Status; yrs=years.

Appendix 3

Proposed MUHC Protocol for the 'Mitoxantrone treatment of patients with aggressive multiple sclerosis (MS)'

Rational: A clinical need exists in our community to implement safe and effective therapies for patients with MS that is not responsive to currently available immune-modulators or MS that is particularly aggressive. In Europe and the USA, Mitoxantrone (Novantrone®) has been approved for the treatment of secondary progressive MS (SPMS), and for patients with rapidly deteriorating relapsing remitting MS (RRMS). Here, we propose a protocol to evaluate the safety and efficacy of Mitoxantrone in patients with aggressive MS.

Mitoxantrone: A synthetic antineoplastic anthracenedione for IV use.

Inclusion criteria*:

- 1- Diagnosis of MS made by a neurology expert and considered aggressive, as defined by:
 - (i) Failure of treatment while on one of the approved immune-modulators (IFN/GA), This is defined as:
 - 2 or more attacks in the preceding year, OR
 - 1-point EDSS confirmed progression within one year (EDSS up to 6.0), OR
 - 0.5-point EDSS confirmed progression within one year (EDSS 6 or greater), OR
 - Progressive loss of upper extremity, bulbar or cognitive function in wheelchair-bound patient. N.B.: progression has to be confirmed on two consecutive examinations, 3 months apart.
 - (ii) Rapidly deteriorating RRMS (not treated), defined as:
 - 2 or more confirmed relapses within a year AND
 - Accrual of significant deficits in motor AND/OR cerebellar functional systems with confirmed loss (3 months apart) of 2 or more points on the EDSS
 - (iii) Rapidly deteriorating progressive MS (not treated), with or without relapses, defined by:
 - Evidence for significant progression in EDSS of at least 1 point in the last 12 months, OR significant worsening in upper extremity, bulbar or cognitive functioning in the preceding year, confirmed on 2 consecutive exams, 3 months apart.
- 2- Consultation to and approval by one member of the panel of MS clinic neurologists involved in the care and f/u of those patients.

* Patients should be evaluated for participation in ongoing clinical trial protocols and, if eligible, participation in such trials should be considered.

Exclusion criteria:

- 1- Failure to meet inclusion criteria
- 2- Significant cardiac dysfunction (including EF < 55 on screening study: MUGA scan)
- 3- Significant pulmonary, renal, hepatic or other organ impairment.
- 4- Significant hematologic disease, defined as presence of myelodysplasia or neutropenia < 1.4 /L or thrombocytopenia less than 100 /L.
- 5- Patient with active viral or fungal infection.
- 6- Patients with known seropositivity for HIV1, HIV2, Hepatitis B or Hepatitis C.
- 7- Patients with prior history of malignancy, other than basal cell Ca.
- 8- Pregnancy or risk of pregnancy.
- 9- Patients unable to provide written informed consent.

Baseline and Screening studies:

- 1- Hematological: CBC, PT and PTT.
- 2- Cardiac: EKG, MUGA scan.
- 3- Pulmonary: CXR.
- 4- Renal and hepatic: serum studies of renal and hepatic function.

Treatments:

- 1- For SPMS:
 - (i) Monthly IV infusion (over 30-60 minutes) at dose of 12 mg/m², for the first 3 treatments.
 - (ii) Additional treatments every 3 months at a dose of 12 mg/m². A maximal dose of 110mg/m² is suggested.
 - (iii) Antiemetic treatment.
 - (iv) IV infusion of steroids on the same day and prior to Mitoxantrone treatment, with Solumedrol 750-1000 mg in NS.
- 2- For RRMS not on DMD, as rescue therapy:
 - (i) Monthly IV infusion (over 30-60 minutes) at a dose of 12mg/m², monthly for 6 treatments.
 - (ii) Antiemetic treatment and monthly use of steroids as above.

Safety monitoring during treatment:

- 1- Hematologic follow-up: CBC and differential before every Mitoxantrone infusion. If neutrophils are below 1.4/L, the dose of mitoxantrone is postponed.
- 2- Cardiac follow-up: MUGA scan at 50, 75 and 100 mg/m² and 6 months post-treatment completion.

Anticipated side effects or Toxicities:

- 1- Hypersensitivity / allergic reaction.
- 2- IV insertion discomfort. Leakage of mitoxantrone may result in tissue damage.
- 3- Nausea and/or vomiting, during and up to several days following infusion.
- 4- Urine and sclera may turn slightly blue for few days following each infusion.
- 5- Lowered white cell counts is expected. This may increase risk of infections.
- 6- Hair loss or thinning may occur; almost always temporary.
- 7- Fertility may be affected. Irregular or absent menses may occur.
- 8- Heart failure may occur in a small percentage of patients due to a toxic cardiomyopathy, Dose related (2 % in a large French cohort followed between 1992-2001).
- 9- Acute myelogenous leukemia (AML), 0.25% in the same French cohort.

Clinical monitoring:

- 1- Review of medical history, adverse events and cardio-vascular examination. before each treatment cycle with mitoxantrone.
- 2- Periodic f/u visits with the neurologist, every 3 to 6 months, for interim MS and relapse history, review of medications, neurological exam and EDSS.

MRI monitoring:

An MRI should be done at baseline and ideally repeated yearly for the duration of the treatment.

MNH/MUHC
July 2002

Appendix 4

Direct Costs to MUHC of mitoxantrone treatment of One Patient.

Additional costs not charged to MUHC shown in parenthesis ().

Evaluation

Item	Unit Cost,\$	Frequency	Total Cost
Clinic visit (Nursing only)	167.08	2	334.16
MD Fees.Consultation †	57.48	1	(57.48)
<u>Lab Tests</u>		1	
Specimen Procurement, per visit	6.22		6.22
CBC(Compl blood count,platelets)	4.98		4.98
INR(International normalized ratio)	4.13		4.13
Serum Albumen	0.59		0.59
Serum Alkaline Phosphatase	0.61		0.61
Serum ALT(alanine amino transferase)	0.67		0.67
Serum bilirubin.Direct,Total	1.33		1.33
Serum Creatinine	4.95		4.95
ECG (technical)	12.00	1	12.00
(professional)†	1.13		(1.13)
Nuclear.MUGA scan (technical)	75.00	1	75.00
(professional)†	34.00		(34.00)
Radiography.Chest (technical)	23.40	1	23.40
(professional)†	4.75		(4.75)
MRI head (technical)	463.00	1	463.00
(professional)†	106.26		(106.26)
TOTAL COST, including professional fees.....			1,134.66
TOTAL COST to MUHC.....			931.04.

† RAMQ. Not charged to MUHC.

Treatment SPMS

Item	Unit Cost \$	Frequency	Total Cost
<u>Day hosp</u>			
Nurse+Pharmacist	226.08	10(mths1,2,3,6,9, 12,15,18,21,24)	2260.80
Mitoxantrone 20 mg	207.72	10	2077.20
Preparation	16.71	10	167.10
IV Solumedrol 1000 mg	15.71	20(days before& of inf)	314.20
Preparation	16.71	20	334.20
Antiemetic*	6.96	10	69.60
CBC,platelets	4.98	10(before infusions)	49.80
MUGA scan (technical)	75.00	4(6 monthly)	300.00
(professional)†	34.00		(136.00)
MRI Head (technical)	463.00	2 (at 1 & 2 years)	926.00
(professional)†	106.26		(212.52)
MD fees†			
Follow up	18.00	10	(180.00)
Neurologist consultation	50.00	8	(400.00)
TOTAL COST,including professional fees.....			7,427.42
TOTAL COST to MUHC.....			6,498.90

† RAMQ. Not charged to MUHC.

Treatment RRMS

Day hospital

Nurse+.Pharmacist	226.08	6(monthly for 6 mths)	1,356.48
Mitoxantrone 20 mg	207.72	6	1,246.32
Preparation	16.71	6	100.26
IV Solumedrol 1000 mg	15.71	6	94.26
Antiemetic*	6.96	6	41.76
CBC Platelets	4.98	6	29.88
MUGA scan (technical)	75.00	2	150.00
(professional)†	34.00		(68.00)
MRI Head (technical)	463.00	1(at 1 year)	463.00
(professional)†	106.26		(106.26)
<u>MD fees †</u>			
Follow up	18.00	6	(108.00)
Neurologist consultation	50.00	2	(100.00)
TOTAL COSTS, including professional fees.....			3,864.22
TOTAL COSTS to MUHC.....			3481.96

† RAMQ. Not charged to MUHC

*Antiemetic: Assume, metoclopramide 10 mg iv(\$0.8)+diphenhydramine 50 mg (\$0.78) before all infusions, with ondansetron 8mg oral(\$10.76) for 50% of cases = \$6.96 on average.