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**THE USE OF MITOXANTRONE IN THE TREATMENT OF  
PATIENTS WITH MULTIPLE SCLEROSIS**

**REPORT UPDATE**

**An update of TAU report Number 3, entitled,  
“SHOULD THE MUHC USE MITOXANTRONE in the TREATMENT OF MULTIPLE  
SCLEROSIS?”**

**Report available at**

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### Abbreviations

EF – ejection fraction

GD - gadolinium

LVEF – left ventricular ejection fraction

MUGA – multiple gated acquisition

PPMS – primary progressive multiple sclerosis

PRMS – progressive-relapsing multiple sclerosis

RCT – randomized controlled trial

SD - standard deviation

SPMS – secondary progressive multiple sclerosis

MS – multiple sclerosis

## **EXECUTIVE SUMMARY**

Mitoxantrone is an antineoplastic agent that is used for the treatment of certain forms of multiple sclerosis (MS) namely secondary-progressive (SPMS), progressive-relapsing (PRMS) or worsening relapsing-remitting (RRMS).

The objective of this report is to review new evidence on the clinical and safety aspects of mitoxantrone treatment in MS patients since the original TAU report of December 2002.

No new clinical comparative studies in a general MS population published since the original report were identified in the literature. However, recent studies that evaluated the use of an induction treatment with mitoxantrone in a subgroup of patients with aggressive MS showed promising results. There are new reports of drug associated cardiotoxicity and acute leukemia with the use of mitoxantrone for the treatment of MS. This increased evidence has prompted the drug manufacturer to issue a letter warning healthcare professionals of the risks of these side effects.

Based on the pooled results of the studies identified in our systematic review, we estimated the risk of cardiac toxicity, as defined by significant decreases in the left ventricular ejection fraction (LVEF), to be 3.9% (number needed to harm 25). Our pooled analysis also revealed a 0.4% risk of developing congestive heart failure (CHF), with rates varying between 0 and 4% among the publications. It was unfortunately not possible to determine the cause of this heterogeneity. Long-term risks beyond 3 years have not been systematically reported and the possibility of delayed cardiotoxicity is not known.

The risk of development of leukemia, based on our pooled analysis was 0.15%.

A review of the records of 55 MS patients treated with mitoxantrone at the MUHC revealed that approximately 25% of the patients experienced depressed left ventricular function, characterized by either a drop to < 50% or a 10% absolute drop from the baseline LVEF value. No cases of congestive heart failure were identified. There was one case of

leukemia among these patients that may have been due to the treatment with mitoxantrone.

The cost of the mitoxantrone treatment in MS patients at the MUHC remains unchanged since the original report, i.e., approximately \$5,000 per patient treated, at a total of \$100,000 if 20 patients are treated.

## **CONCLUSIONS**

**Since the last report no new evidence indicating more substantial or more permanent benefit of mitoxantrone treatment in a general MS population has been identified.**

**Further evidence of cardiotoxicity even at relatively low doses has been identified. There are also new reports suggesting increased risk of leukemia.**

**Three recent case studies report excellent results of mitoxantrone induction treatment in patients with highly aggressive forms of MS but suffer from a lack of any comparator group.**

**For these reasons the present indications for use use of mitoxantrone in MS should be reconsidered.**

## **RECOMMENDATIONS**

**Reports of treatment benefits in aggressive forms of RRMS or SPMS are sufficiently promising to justify its continued study at the MUHC in the context of an observational phase IV data collection to systematically record disease progression and toxic side effects.**

**Aggressive forms of M. S. are defined as:**

**1) The occurrence of two relapses, with sequelae, in the 12 months preceding the initiation of mitoxantrone therapy, AND one new gadolinium-enhanced lesion on the MRI in the 3 months preceding the initiation of mitoxantrone therapy whenever possible. (It is recognized that the MRI criterion may not always be applicable at the MUHC).**

**OR**

**2) Deterioration of 2 points in the EDSS score in the 12 months preceding the initiation of mitoxantrone therapy, AND 1 new gadolinium enhanced lesion on the MRI in the 3 months preceding the initiation of mitoxantrone therapy.**

**The rigorous documentation of pre-treatment clinical progression (EDSS change, relapse rates) with gadolinium-enhanced MRI Imaging whenever possible, should be maintained, and continued, during treatment and long-term follow-up so that the experience gained can be eventually added to the knowledge base.**

**The subsequent use of other cardiotoxic drugs such as cyclophosphamide should be accompanied by cardiac monitoring.**

**Treatment should only be initiated after full discussion with patients of the limited and uncertain benefits to be expected, the absence of knowledge of the duration of these effects, and the possibility of serious side effects. It is recommended that signed informed consent be obtained.**

**It is suggested that the contents of this report be shared with referring physicians with the objective of discouraging mitoxantrone therapy except for those cases most likely to benefit. The MUHC should not authorize any increase in patients above the present threshold of 20 per year.**

## THE USE OF MITOXANTRONE IN THE TREATMENT OF PATIENTS WITH MULTIPLE SCLEROSIS – REPORT UPDATE.

### FOREWORD

Mitoxantrone was initially introduced as an antineoplastic agent<sup>1</sup> and in 2000 it was approved by the United States Food and Drug Administration (FDA)<sup>2</sup> for secondary progressive (SPMS), progressive relapsing (PRMS), or worsening relapsing-remitting (RRMS) multiple sclerosis . Multiple sclerosis is not included in the approved labeled indications for mitoxantrone in Canada<sup>3</sup>.

On December 2<sup>nd</sup> 2002 the Technology Assessment Unit (TAU) submitted a report to the MUHC entitled “Should the MUHC use mitoxantrone in the treatment of multiple sclerosis?”<sup>4</sup>. The report reviewed the clinical benefits and side effects of this therapy, in particular the risk of cardiotoxicity and leukemia. It concluded that although the clinical benefits to be expected were not substantial and had not yet been shown to be permanent, they were still sufficient to justify use of mitoxantrone for certain patients. It recommended that a limited programme of up to 20 new treatment enrollments per year should be approved, but stipulated that this decision should be reviewed in the light of the *experience accumulated*, and of any *new evidence concerning benefits and side effects* of mitoxantrone and of *competing treatments* (see appendix 1).

In April 2005, due to drug safety concerns, the FDA and the manufacturer of Novantrone® (mitoxantrone) sent a letter to healthcare professionals issuing a box warning for both cardiac toxicity and secondary acute myeloid leukemia (AML)<sup>5</sup>.

The objective of the current document is to examine the evidence concerning the benefits and toxicity of mitoxantrone in multiple sclerosis patients published since the original report<sup>4</sup>.

## **INTRODUCTION**

Multiple sclerosis is a chronic disabling central nervous system disease that affects young adults<sup>6</sup>. The clinical evolution of the disease is characterized by irreversible limitation in ambulation, unilateral aid for walking, and wheelchair use requirement after a median of 8, 20, and 30 years from onset respectively, with nevertheless a low impact on life expectancy<sup>6</sup>.

One of the aims of treatment is to prevent disease progression and relapses, drugs used with this objective are referred to as disease-modifying drugs<sup>7</sup>. Other treatments such as steroids are used to treat acute exacerbations of the disease<sup>7</sup>.

Mitoxantrone, a disease-modifying drug is approved by the FDA and European countries for treatment of secondary progressive (SPMS), progressive-relapsing (PRMS) and relapsing-remitting multiple sclerosis (RRMS)<sup>2 8 9</sup>. This drug, which possesses anti-inflammatory and immunosuppressive properties<sup>10</sup>, was approved in France in 2003 as a second-line treatment for patients with an aggressive form of multiple sclerosis<sup>A 11</sup>. This aggressive form of the disease may have a better response to mitoxantrone therapy as it seems to be associated with an inflammatory process rather than a secondary degenerative process<sup>9</sup>.

Sixty-five to eighty-five percent of the new patients present with RRMS, and more than half of these patients evolves to SPMS<sup>12 13</sup>. Approximately 10% of the new patients presents with another form of the disease, primary progressive multiple sclerosis (PPMS)<sup>12</sup>. The least common form of the disease is PRMS<sup>12</sup>.

## **METHODS**

### **Literature Review**

A literature review was performed through PUBMED, EMBASE, INAHTA, and Cochrane databases in order to identify clinical and observational studies, technology assessment

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<sup>A</sup> Aggressive multiple sclerosis: RRMS or SPMS defined by 1) 2 relapses both with sequelae in the preceding 12 months and a new lesion (Gd-enhanced on MRI) not older than 3 months OR 2) Progression of 2 points in the EDSS scale in the preceding 12 months and 1 new lesion (Gd-enhanced on MRI) not older than 3 months<sup>11</sup>.

reports, and case-reports with mitoxantrone in multiple sclerosis patients. Websites of conferences in the field were also searched in order to identify new safety and efficacy information on mitoxantrone. Search terms included “mitoxantrone” and “multiple sclerosis”(MS). A search using the term “multiple sclerosis” individually was also carried out in an attempt to identify clinical studies on new therapies for patients with multiple sclerosis. Studies in humans published in English or French were selected. Clinical studies and technology assessment reports were included if they were published after the original TAU report, however case-reports on drug toxicity were included even if published before the initial TAU report. The search was last updated on May 09<sup>th</sup> 2006.

In August 2004 a review of the status of mitoxantrone treatment for MS and a summary of local experience was carried out by a committee of the Montréal Neurological Institute (MNI), under the chair of Dr. J. Stewart [Stewart committee]<sup>14</sup>. This invaluable document was used as a data source and was supplemented when necessary by personal communication with Dr. Yves Lapierre.

### **Hospital Chart Review**

In order to assess local safety of mitoxantrone, a chart review was performed. This permitted an evaluation of how closely patients followed the established mitoxantrone administration protocol and of drug toxicity, especially cardiac toxicity. A drop in LVEF was defined as a drop to below 50% or an absolute drop of at least 10% from the baseline measurement. Only patients who started the mitoxantrone treatment before July 2005 were reviewed as this would allow enough time for at least two LVEF exams to be performed, i.e., baseline and first on-treatment follow-up examination (as per the MS clinic protocol).

### **RESULTS**

No additional randomized controlled trials (RCTs) on the clinical outcomes of mitoxantrone in patients with multiple sclerosis were identified in the peer-reviewed literature since the December 2002 TAU report. However, some case reports of toxicity were identified, as described below. The search did not yield any clinical studies of new disease-modifying drugs with regulatory approval for patients with multiple sclerosis. However, several new

agents are in their early phase of development<sup>15</sup>. Natalizumab, a drug approved by the FDA for relapsing forms of multiple sclerosis in November 2004<sup>2</sup> was withdrawn from the market three months later due to safety concerns<sup>16</sup>. Since February 2006 natalizumab has been allowed for use only in patients with relapsing-remitting multiple sclerosis who had been previously treated with the drug in clinical trials<sup>17</sup>. As it is presently not known if marketing of the drug will be fully resumed and as no clinical studies comparing natalizumab with mitoxantrone were identified in the literature, we have not included results of studies with this drug in our report.

One Clinical Guideline from the National Institute of Clinical Excellence (NICE) from the UK on the management of multiple sclerosis was published<sup>18</sup> and one systematic review that included previously published RCTs was identified<sup>19</sup>. One non-comparative observational study in patients with SPMS treated with either mitoxantrone or cyclophosphamide was identified<sup>20</sup>. Three new publications in patients with aggressive forms of the disease were identified<sup>21 22 23</sup>.

Publications relating to cardiotoxicity consisted of one pooled analysis of three previously published studies<sup>24</sup>, one RCT not included in the pooled analysis<sup>25</sup>, 14 observational studies<sup>21 26 27 28 29 30 31 32 33 34 35 36 37 38</sup>, and one case-report<sup>39</sup>. Three observational studies<sup>27 40 41</sup>, one pooled analysis of three previously published studies<sup>42</sup>, and ten case reports of secondary AML following the use of mitoxantrone were also identified<sup>39 43 44 45 46 47 48 49 50 51</sup>. A publication reported the findings of an observational study of mitoxantrone in MS patients and it includes information both on cardiotoxicity and leukemia<sup>52</sup>. The RCTs included in the systematic review<sup>19</sup> and toxicity pooled analyses<sup>25 42</sup> mentioned above had already been included in the original TAU report<sup>4</sup>.

The findings of these publications are summarized below.

In July 2003, the Agence Française de Sécurité Sanitaire des Produits de Santé (Afssaps) issued a letter to neurologists and hematologists warning about the occurrence of cases of leukemia in MS patients treated with mitoxantrone<sup>53</sup>. Afssaps also warns about other risks

associated with mitoxantrone treatment such as cardiac toxicity and fertility problems and gives recommendations on toxicity monitoring before, during and after treatment<sup>53</sup>. It is stipulated in the letter that patients be informed of the toxicity profile of mitoxantrone before starting treatment<sup>53</sup>. The French agency also requires that patients sign a document confirming that they were informed about the toxicity of mitoxantrone and that they agree to be treated with the drug<sup>11</sup>.

In April 2005, due to drug safety concerns based on information received from post-marketing surveillance, spontaneous adverse event reports, peer-reviewed literature and information from an ongoing observational study, the FDA and the manufacturer of Novantrone® (mitoxantrone) sent a letter to healthcare professionals issuing a box warning for both cardiac toxicity and secondary acute myeloid leukemia (AML)<sup>5</sup>.

### **Efficacy**

The literature review revealed no new comparative clinical studies of the efficacy of this treatment. The longest follow-up yet reported is 3 years in the placebo controlled RCT by Hartung et al.<sup>54</sup>.

The clinical guidelines published by NICE in November 2003 stated that mitoxantrone should only be used in patients with RRMS or SPMS in specific circumstances: 1) after full discussion and consideration of all risks, 2) with formal evaluation (preferably in a randomized or prospective study), and 3) by an expert in the use of these medicines in MS<sup>18</sup>.

Both the recommendations from the NICE clinical guidelines<sup>18</sup> and the recommendations of a systematic review<sup>19</sup> (that included RCTs that had already been included in the original TAU report) arrived at similar conclusions to those of the original TAU report<sup>4</sup> regarding the efficacy of mitoxantrone and the need for further clinical surveillance and evaluation.

One non-randomized study including 50 patients with SPMS treated with mitoxantrone or cyclophosphamide was identified<sup>20</sup>. The study found a reduction in the mean rate of

relapse after the end of treatment compared to baseline for both drugs, i.e.,  $2.1 \pm 1.8$  vs.  $0.25 \pm 0.4$  ( $p=0.001$ ) for mitoxantrone, and  $2.2 \pm 1.9$  vs.  $0.3 \pm 0.5$  for cyclophosphamide ( $p=0.003$ )<sup>20</sup>. There was improvement in the mean EDSS score from baseline to 2 years after the start of therapy in both groups, i.e., 5.4 vs. 4.6 ( $p=0.01$ ) for mitoxantrone, and 5.7 vs. 4.8 ( $p=0.02$ ) for cyclophosphamide<sup>20</sup>. Nineteen (76%) out of 25 patients in the mitoxantrone group had either no change or an improvement in the EDSS score, in the cyclophosphamide group, 23 (92%) of the patients had the same endpoint<sup>20</sup>. The outcomes in the two treatment groups cannot be compared as the study was not randomized and as there were differences in the baseline values between the two groups.

### **Patients with aggressive MS**

Two clinical observational studies with a follow-up of 2 years<sup>21</sup> and 3.8 years (median)<sup>22</sup> and one study evaluating the MRI changes in patients with aggressive MS treated with mitoxantrone<sup>23</sup> have been published since the last report.

**Le Page et al 2006**. This observational study evaluated mitoxantrone induction treatment in 100 patients with aggressive RRMS (6 monthly administrations of  $12\text{mg}/\text{m}^2$  of mitoxantrone with 1000 mg methylprednisolone)<sup>21</sup>. The average annual relapse rate in the year prior to the mitoxantrone induction treatment (3.20,) fell to 0.30 during the first year of treatment ( $p<0.00001$ )<sup>21</sup>. The proportion of patients showing deterioration fell from 87% in the year prior to the induction treatment to 4% at the end of the first year ( $p<0.000001$ )<sup>21</sup>. The proportion of patients with gadolinium (Gd)-enhanced lesions on MRI decreased from 84% before mitoxantrone to 9% at one year after the treatment started<sup>21</sup>. According to the authors, at the end of the five years of follow-up, some of the early benefits observed were maintained such as reduced frequency of relapses<sup>21</sup>. The improvement in EDSS score was maintained until the 4<sup>th</sup> year and the percentage of patients not experiencing deterioration was 89% at 2 years, and 79% at 3 years<sup>21</sup>. More details are shown in Appendix 2.

The study presents a long-term follow-up in a specific group of patients with a more active form of the disease<sup>21</sup>, however, not all patients were followed for more than 1-2 years.

**Correale et al 2006.** This observational study included 10 patients who met the criteria for aggressive RRMS while receiving treatment with interferon beta<sup>22</sup>. Patients received induction treatment with mitoxantrone 12mg/m<sup>2</sup> and methylprednisolone 1000 mg monthly for 3 months followed by treatment with interferon beta<sup>22</sup>. There was a decrease in the number of relapses and new Gd-enhanced lesions on MRI measured after the mitoxantrone induction treatment compared to the preceding 6 months<sup>22</sup>. The number of Gd-enhanced lesions on MRI was 7± 1.9 before treatment, 0.5 ±0.7 immediately after mitoxantrone treatment (p=0.002), and 2.7 ±3.9 6 months after the end of mitoxantrone treatment<sup>22</sup>. The number of relapses decreased from 3.2 ±0.4 before treatment to 0.9 ±1.3 1-6 months after the end of mitoxantrone treatment (p=0.004)<sup>22</sup>. The EDSS remained stable during the mitoxantrone induction treatment, 3.4 ± 0.7<sup>22</sup>. The EDSS had been worsening before the start of mitoxantrone treatment, i.e., 2.2 ±0.9 to 3.4 ±0.7<sup>22</sup>.

The number of relapses (0.4 ± 0.5), Gd-enhanced lesions on MRI (0.16 ± 0.4), and EDSS score (3.0 ± 0.8) 24 months after the end of the induction treatment did not differ significantly from the values observed during induction treatment in the seven patients considered as interferon-beta responders<sup>22</sup>. The responders received 15-18 months of interferon-beta treatment<sup>22</sup>. The three non-responders' condition worsened during interferon-beta therapy, i.e., relapse rates increased from 0 after mitoxantrone treatment to 2.7±0.6 during interferon-beta treatment, EDSS worsened from 3.4±0.7 to 5.3 ±0.3, and the number of Gd-enhanced lesions increased from 0.5 ±0.7 to 3.3 ±1.1 during the same period<sup>22</sup>. Mitoxantrone treatment was re-started in these patients at 3-month intervals and after an additional 15-18 months of follow-up, the EDSS was stabilized (5±0.5) and no new relapses or new Gd-enhanced lesions were observed<sup>22</sup>. More details in Appendix 2.

The study included only 10 patients<sup>22</sup>, nevertheless, this study<sup>22</sup> suggests, as did the study by Le Page et al.<sup>21</sup>, that induction treatment with mitoxantrone given concomitantly with methylprednisolone may be beneficial in patients with highly active RRMS<sup>22 21</sup> due to the control of the inflammatory process of the disease<sup>21</sup>. The authors of these studies also believe that mitoxantrone controls the inflammatory process beyond the induction treatment

period and that patients can continue to receive other MS therapies after the induction period<sup>22 21</sup>.

**Krapf 2006** A substudy of an RCT comparing mitoxantrone and placebo in patients with active SPMS or worsening RRMS (MIMS study included in the original report<sup>54</sup>) evaluated the changes in unenhanced and Gd-enhanced MRI in 188 patients<sup>23</sup>. The group of patients receiving mitoxantrone 12mg/m<sup>2</sup> had a reduced number of T2-weighted lesions at month 24 (p=0.027) compared to placebo<sup>23</sup> (0.29 vs. 1.94 respectively). There was a trend towards a reduction in the number of active lesions at month 24 for the mitoxantrone 12mg/m<sup>2</sup> group compared to placebo, and no difference between placebo and mitoxantrone were observed in the total of MRI scans with positive Gd enhancement<sup>23</sup>.

## **Toxicity**

### **Myocardial injury**

Because the complications of mitoxantrone therapy are more difficult to determine in the presence of malignancy and the associated therapeutic interventions directed to its control, Ghalie and colleagues pooled the results from three clinical trials in which mitoxantrone was used for the treatment of MS<sup>24</sup>. The total number of patients in this pooled analysis was 1378 (median 29 months from the start of therapy), and the mean cumulative dose of mitoxantrone was 60.5 mg/m<sup>2</sup> (range 2-183 mg/m<sup>2</sup>)<sup>24</sup>. The analysis showed that two patients developed heart failure (0.15%)<sup>24</sup>. Of 779 patients who completed treatment and follow-up 17 (2.18%) had asymptomatic reductions of left ventricular ejection fraction (LVEF) <50%<sup>24</sup>. There was a trend to a higher risk of this complication among patients who received a dose higher than 100 mg/m<sup>2</sup>, i.e., 5%, compared to patients who received a lower dose, 1.8% (p=0.06)<sup>24</sup>.

Four-year follow-up (mean cumulative dose of 77mg/m<sup>2</sup>) of one of the original studies included in the pooled analysis by Ghalie et al.<sup>24</sup> (n=802) reported one new case (0.1%) of acute clinical heart failure and 20 new cases (total of 33 (4.2%)) of asymptomatic decrease of LVEF to less than 50%<sup>27</sup>. A more recent abstract after 5 years of follow-up reported 4

additional cases of asymptomatic decrease of LVEF to < 50% (total of 37 (4.7%))<sup>28</sup>. This continuing escalation in the heart failure cases with longer follow-up is disconcerting, especially as the cumulative doses remained stable at 77 mg/m<sup>2</sup>.

One author observed that 8 out of 68 (11.7%) multiple sclerosis patients treated with mitoxantrone showed either a decrease in LVEF to below 50% or a decrease of at least 10% from baseline, 3 of which (38%) were observed with doses between 94 and 120 mg/m<sup>2</sup> and the remaining 5 (62%) patients with cumulative doses above 120 mg/m<sup>2</sup><sup>36</sup>.

The preliminary results of an ongoing observational study to evaluate the safety of mitoxantrone in 509 MS patients are reported in the review of Cohen and Mikol<sup>52</sup>. With a mean therapy duration of 1.2 years (0-2.8), and a mean cumulative dose of 59.7 mg/m<sup>2</sup>, so far two (0.39%) cases of CHF and 23 (4.5%) cases of asymptomatic LVEF decrease (>= 10%) have been observed<sup>52</sup>.

Altogether, in 16 studies (see table 1), with cumulative mitoxantrone doses ranging from 37.5 to 207 mg/m<sup>2</sup>, and with a duration of follow-up (not reported in 8 cases) ranging from 1.2 to 4 years, there was an overall 0.41% rate of development of symptomatic CHF, and a 3.8% rate of decrease in LVEF, defined by either a LVEF drop below 50% or a decrease of more than 10% from baseline (Table 1). However, there is also some evidence of later development of LV dysfunction since Goffette et al. reported in a conference that 3 out of 69 (4.3%) patients studied have developed congestive heart failure 24 - 80 months after the end of treatment with mitoxantrone<sup>30</sup>, leading us to conclude that while the long-term effects of this drug on cardiac function are still somewhat uncertain, they are not completely benign.

The large variation in the reported rates of cardiotoxicity among the different studies is difficult to explain based on the information provided. The roles of other concurrent cardiotoxic medications, such as cyclophosphamide<sup>27 30 55</sup>, and possible underlying occult heart disease remain uncertain<sup>55 56 57</sup>. Clearly asymptomatic deterioration of LV function occurs more frequently than frank congestive heart failure. Longer-term follow-up is

required to determine the late incidence of LV dysfunction and the risk of progression to congestive heart failure.

Table 1 - Cardiotoxicity in MS patients treated with mitoxantrone

| Study (year)<br>N   | Follow-up<br>(median/<br>mean)  | Cumulative<br>Mitoxantrone dose<br>(median/mean)  | New cases of<br>symptomatic CHF   | Decrease in LVEF   |
|---|---|---|---|--|
| Ghalie et al. <sup>24</sup> (2002)<br>Pooled analysis¶<br>N=1,378   | 2.4 years   | 62.5 mg/m <sup>2</sup> (mean)<br>(range 2-183)  | 2 (0.15%)   | LVEF < 50% (n=779*)<br>17 (2.18%)  |
| Edan et al. <sup>**27</sup> (2004)<br>Observational study<br>(N=802 Extension from<br>the results in Ghalie et<br>al. <sup>24</sup> ) | 4 years   | 77 mg/m <sup>2</sup> (mean)<br>120 mg/m <sup>2</sup> dose in<br>patient who<br>developed acute<br>heart failure <sup>30</sup>         | 1 (0.13%) acute clinical heart<br>failure – not previously<br>reported <sup>24</sup><br>previous use of<br>cyclophosphamide <sup>30</sup> | LVEF < 50% (n=786*)<br>20 new events<br>In total there were 33 events (4.2%), i.e., 13<br>previously reported <sup>24</sup> . Persistent in 8 patients<br>(1%) |
| Le Page et al. <sup>** 26</sup> (2004)<br>Observational study<br>(N=802 Extension from<br>the study by Edan et al. <sup>27</sup> )    | 5 years   | 77 mg/m <sup>2</sup> (mean)   | 1 (0.13%) acute clinical<br>heart failure – previously<br>reported <sup>27</sup>  | LVEF < 50% (n=788*)<br>4 new events<br>In total there were 37 events (4.7%), i.e., 33<br>previously reported <sup>24 27</sup>                                  |
| Van de Wyngaert et al. <sup>25</sup><br>(2001)<br>RCT / N=28<br>(mitoxantrone)<br>N=21 (MP)   | 3 years   | 60 mg/m <sup>2</sup> and 84<br>mg/m <sup>2</sup> (after 11<br>and 17 months of<br>treatment in 2<br>patients with<br>cardiotoxicity)§ | 0   | LVEF < 50% (N=28)<br>2 (7.1%)<br>No case observed in the methylprednisolone<br>group   |
| Cohen & Mikol <sup>52</sup> (2004)<br>Observational study<br>N=509 (preliminary report<br>of registry study)                          | 1.2 years   | 59.7 mg/m <sup>2</sup><br>(mean)  | 2 (0.39%)   | LVEF decrease >= 10% from baseline<br>23 (4.5%)  |
| Gonsette <sup>36</sup> (1996)<br>Observational study<br>N=68  | -   | 94 – 207 mg/m <sup>2</sup><br>(in patients with<br>cardiotoxicity)  | 1 (1.5%)<br>cumulative dose: 207<br>mg/m <sup>2</sup><br>Previous use of lithium  | LVEF < 50% or decrease >= 10% from<br>baseline<br>8 (11.7%)  |
| Avasarala et al. <sup>26</sup> (2003)<br>Observational study<br>N=28  | LVEF<br>evaluation<br>from<br>baseline to<br>before 4 <sup>th</sup><br>dose | 37.5 mg/m <sup>2</sup><br>(patients with<br>cardiotoxicity)   | 0   | LVEF decrease >= 10% from baseline<br>5 (17.8%)  |
| Montu et al. <sup>29</sup> (2004)<br>Observational study<br>N=18  | -   | 12 and 24 mg/m <sup>2</sup><br>(in 2 patients with<br>cardiotoxicity)   | 0   | 2 (11%) – acute cardiotoxicity with severe<br>decrease of LVEF.<br>No late cardiotoxicity  |
| Goffette et al. <sup>30</sup> (2004)<br>Observational study<br>N=52<br>18 (35%) previous<br>cyclophosphamide                          | -   | 144 mg/m <sup>2</sup> (in<br>patients with<br>cardiotoxicity)   | 3 (4.3%) congestive heart<br>failure of late onset (24-80<br>m after end of treatment)<br>(prior cyclophosphamide: 2<br>patients)         | Acute cardiotoxicity – None  |
| Adoni et al. <sup>31</sup> (2004)<br>Observational study<br>N=25  | -   | 78 mg/m <sup>2</sup><br>(mean)  | 0   | 0  |
| Mannechi et al. <sup>32</sup> (2004)<br>Observational study<br>N=30   | -   | -   | 0   | 4 (13%) - does not specify how much it<br>dropped  |
| Kkolou et al. <sup>33</sup> (2003)<br>Observational study =49   | -   | -   | 0   | 1 (2%) – does not specify how much but<br>treatment had to be discontinued   |
| Benesova and Stourac<br><sup>34</sup> (2003)<br>Observational study =33   | -   | -   | 0   | 0  |
| Zingler <sup>35</sup> (2005)<br>Observational study =70   | 2 years   | 114 mg (mean)   | 0   | 0  |

Table 1 – (cont.)

| Study (year)<br>N   | Follow-up<br>(median/<br>mean)                             | Cumulative<br>Mitoxantrone dose<br>(median/mean)  | New cases of<br>symptomatic CHF   | Decrease in LVEF   |
|---|--|---|---|--|
| Ostberg et al. <sup>37</sup> (2005)<br>Observational study<br>N=31  | -  | > 20 mg/m <sup>2</sup> (in<br>patients with<br>cardiotoxicity)  | 0   | 4 (13%)  |
| Le Page et al. <sup>21</sup> (2006)<br>Observational study<br>N=100 | 3.8 years  | 82, 113 and 116 mg<br>/m <sup>2</sup> in the 3 patients<br>with LVEF drop<br>Diagnoses 1 month –<br>5 years after the last<br>administration  | 1(1%) case of transitory<br>symptomatic LVEF<br>decrease                                  | 3/100 (3%)<br>3/66 (4.5%) if only patients with at least 3<br>years of follow-up are included. |
| Hamzehloo A. <sup>38</sup> (2006)<br>Observational study<br>N=96    | 1 year   | 24mg/m <sup>2</sup> and<br>36mg/m <sup>2</sup> in 2 and<br>1patient respectively<br>who had a drop in<br>LVEF, N/A in the<br>other 3 patients<br>(maximum dose was<br>60mg/m <sup>2</sup> ) | 0   | LVEF < 50% or decrease >= 10%<br>6 (6.3%)  |
| <b>Pooled results<br/>(weighted average)<br/>N=2,515</b>            | <b>1.2-4 years<br/>(not<br/>reported in<br/>6 studies)</b> | <b>59.7-144 mg/m<sup>2</sup><br/>(not reported in 4<br/>studies)</b>  | <b>10 (0.40%)<br/>5 (0.21%) – excluding 3<br/>with prior<br/>cyclophosphamide<br/>use</b> | <b>LVEF &lt; 50% or decrease &gt;= 10%<br/>99 (3.9%)</b>                                       |

\* Patients with follow-up information

\*\* Study was part of the pooled analysis by Ghalie et al.<sup>24</sup>, here we present a follow-up of the data previously reported

§ Cumulative dose calculated according to the mitoxantrone dosing schedule and time of treatment reported in the published study

¶ - The pooled analysis included one randomized study and two retrospective chart review<sup>24</sup>.

LVEF – left ventricular ejection fraction / CHF – congestive heart failure / RCT – randomized controlled trial / MP- methylprednisolone  
N/A = not available

\* Patients with follow-up information

\*\* Study was part of the pooled analysis by Ghalie et al.<sup>24</sup>, here we present a follow-up of the data previously reported

§ Cumulative dose calculated according to the mitoxantrone dosing schedule and time of treatment reported in the published study

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LVEF – left ventricular ejection fraction / CHF – congestive heart failure / RCT – randomized controlled trial / MP- methylprednisolone

Thus, with the passage of time, more evidence of risk of cardiac damage with mitoxantrone therapy has accumulated and there is general agreement that this risk increases with the dose of mitoxantrone administered<sup>24 52 58</sup>. In one 29-year-old patient who received a large total dose of 550 mg of mitoxantrone, approximately 200 mg/m<sup>2</sup>, heart failure was severe and progressive, requiring heart transplantation<sup>59</sup>. However, cardiotoxicity may be seen at much lower dosages. In one clinical study, 5 of 28 patients (17.8%) who had received only 37.5 mg/m<sup>2</sup> demonstrated a fall in LVEF (measured by radionuclide ventriculography) of more than 10%<sup>26</sup>.

Post-marketing surveillance reports of diminished cardiac function with the use of mitoxantrone prompted the FDA and the drug manufacturer to issue a warning letter addressed to healthcare professionals<sup>5</sup>. The manufacturer estimates that symptomatic congestive heart failure (CHF) occurs in 2.6% of the cancer patients who received a

cumulative mitoxantrone dose of up to 140mg/m<sup>2</sup><sup>5</sup>. According to the manufacturer, potentially fatal CHF may occur either during therapy or months to years after the interruption of the treatment<sup>5</sup>. Therefore, it advises that the LVEF should be monitored before and during treatment (LVEF evaluation before each dose is administered to multiple sclerosis patients) in patients with multiple sclerosis who are treated with mitoxantrone (detailed precautions can be found in the letter from the manufacturer)<sup>5</sup>. No recommendations are provided as to the required length of cardiac follow-up. Since the risk of cardiac toxicity appears to increase as the cumulative dose increases, it is recommended that treatment should be discontinued once a cumulative lifetime dose of 140 mg/m<sup>2</sup> is reached<sup>5</sup>. It is suggested that within 2-4 years of follow-up, at least 3.9% of patients will experience cardiotoxicity (Table 1). Information about the clinical significance or reversibility of these cases is not presently available. The concern that cardiotoxicity may occur at doses lower than 140 mg/m<sup>2</sup> is also shared by other authors<sup>60</sup>.

*In summary*, since the original TAU report, there is increased evidence of the occurrence of myocardial toxicity in patients treated for MS. Of the 16 case series reported above, in spite of the moderate dosage schedules, there was evidence of reduced ejection fraction in 11 series, and in five of these there was a reduced EF in more than 10% of the cases treated. Furthermore, although the risk increases with the dose, LVEF may sometimes become depressed at relatively low doses. There is general agreement that LVEF should be measured before and regularly during treatment and that total dose should not exceed 140 mg/m<sup>2</sup>. There is little follow-up beyond two years and late onset myocardial depression is still a possibility.

### Leukemia

One study identified one case (0.2%) of acute myeloid leukemia among 644 multiple sclerosis patients treated with mitoxantrone<sup>40</sup>. The disease onset occurred 28 months after the end of treatment with mitoxantrone, with a total cumulative dose of 84mg<sup>40</sup>.

Preliminary results of an ongoing observational study including 509 MS patients reported in a review by Cohen and Mikol<sup>52</sup> shows that no cases of leukemia have been observed so

far, with a mean therapy duration of 1.2 years (0-2.8), and a mean cumulative dose of 59.7 mg/m<sup>2</sup><sup>52</sup>.

An analysis of data pooled from previously reported clinical studies of mitoxantrone treatment of MS revealed a 0.07% incidence (1/1378 patients) of therapy-related acute leukemia after a median follow-up of 36 months and a median cumulative dose of 60 mg/m<sup>2</sup><sup>42</sup>. However, a more recent publication of one of these studies has reported an additional case of therapy-related leukemia, with a rate of 0.25% (2/802) after a mean follow-up of approximately 4 years<sup>27</sup>.

Pooled together, the studies have shown an incidence of acute leukemia of 0.15% in MS patients treated with mitoxantrone after a follow-up of 1.2-4 years and a mean dose of 60-73 mg/m<sup>2</sup> (table 2). As the FDA letter notes, the rate of secondary leukemia in breast cancer patients treated with mitoxantrone is 1.6% after 10 years. For comparison, the 2005 Canadian population estimated rate of leukemia was 0.008% for females and 0.014% for males<sup>61</sup>.

Table 2 presents the publications that studied the effects of mitoxantrone treatment on the development of acute leukemia in MS patients.

**Table 2 - Acute myeloid leukemia in MS patients treated with mitoxantrone**

| <b>Study (year)<br/>N</b>   | <b>Follow-up<br/>(median/mean)</b>                   | <b>Cumulative<br/>Mitoxantrone dose<br/>(median/mean)</b>       | <b>New cases of acute<br/>Myeloid Leukemia</b>   | <b>Time from end of treatment</b> |
|---|--|---|--|-----------------------------------|
| Ghalie et al. <sup>42</sup> (2002)<br>Pooled analysis<br>N=1,378  | 2.4 years  | 60 mg/m <sup>2</sup> (mean)<br>70 mg/m <sup>2</sup> (patient)   | 1 (0.07%)  | 16 months                         |
| Voltz et al. <sup>40</sup> (2004)<br>Observational study<br>N=644   | 2.7 years  | 48 mg/m <sup>2</sup> (patient)                                  | 1 (0.2%)   | 28 months                         |
| Cohen & Mikol <sup>52</sup><br>(2004)<br>Observational study<br>N=509 (preliminary<br>report)                                 | 1.2 years  | 59.7 mg/m <sup>2</sup> (mean)                                   | 0  | -                                 |
| Edan et al.* <sup>27</sup><br>(2004)<br>Observational study<br>(N=802, already<br>counted in Ghalie et<br>al. <sup>42</sup> ) | 4 years  | 73 mg/m <sup>2</sup> (mean)                                     | 2 (0.25%) – 1 previously<br>reported (ref)   | 20-22 months                      |
| Arruda et al. <sup>41</sup><br>(2004)<br>Observational<br>study N=25  | -  | 12 mg/m <sup>2</sup> (patient)                                  | 1 (4%) – according to<br>the authors, it is not<br>possible to attribute<br>causality to<br>mitoxantrone | 30 months                         |
| Le Page et al. <sup>21</sup><br>(2006)<br>Observational<br>study<br><b>N=100</b>  | 3.8 years  | -   | 0  | -                                 |
| <b>Pooled results<br/>N=2,656</b>   | <b>1.2-4 years (not<br/>reported in 1<br/>study)</b> | <b>60-73 mg/m<sup>2</sup> (not<br/>reported in 1<br/>study)</b> | <b>4 (0.15%)</b>   | <b>16-30 months</b>               |

\* Study by Edan et al.<sup>9</sup> is part of the pooled analysis<sup>42</sup>, here we present a follow-up of the data previously included

Table 3 presents the case-reports of acute leukemia identified. A delay of 5 months to 5 years between the end of treatment with mitoxantrone for MS and the development of therapy-related leukemia was observed in several case reports<sup>39 43 44 45 46 47 48 49 50 58 51</sup>, (table 3). The prognosis of the therapy-related leukemia was considered severe by Gonsette et al. as 3 out of the 7 (43%) cases reported died<sup>58</sup>. The difficulty in interpreting case reports without denominators is obvious. The French government received 8 reports of development of leukemia in MS patients treated with mitoxantrone between 1999 and 2004<sup>53,62</sup>, at least part of these cases may have been included in the case-reports mentioned above.

**Table 3 - Case-Reports of leukemia in MS patients treated with mitoxantrone**

| Author (year)  | Diagnosis                    | Dose  | Cumulative dose                                | Time of diagnosis (after end of treatment) |
|--|------------------------------|---|--|--|
| Heesen et al. <sup>39</sup> (2003)                   | Acute myeloid leukemia       | 12mg/m <sup>2</sup> every 3 months                | 6 courses (72 mg/m <sup>2</sup> )              | 5 months (approximately)                   |
| Cattaneo et al. <sup>43</sup> (2003)                 | Promyelocytic leukemia       | 10mg/m <sup>2</sup> every 3 months for 11 courses | 198mg  | 14 months                                  |
| Brassat et al. <sup>44</sup> (2002) <sup>63 64</sup> | Acute myeloid leukemia       | 20mg every 5 weeks                                | 120mg (66.7 mg/m <sup>2</sup> )                | 15 months                                  |
| Goodkin et al. <sup>45</sup> (2003)                  | Acute myeloid leukemia       | 20 mg once a month                                | 7 courses (140 mg)                             | 3 months (approximately)                   |
| Goodkin et al. <sup>45</sup> (2003)                  | Acute myeloid leukemia       | Not reported                                      | Not reported                                   | Not reported                               |
| Vicari et al. <sup>46</sup> (1998)                   | Acute promyelocytic leukemia | 10 mg/m <sup>2</sup> (5 monthly administration)   | 87.5 mg (50 mg/m <sup>2</sup> )                | 5 years                                    |
| Tanasescu et al. <sup>47</sup> (2004)                | Acute myeloid leukemia       | Not reported                                      | 160 mg   | NR   |
| Delisse et al. <sup>48</sup> (2004)                  | Acute myeloid leukemia       | 20 mg   | 120 mg   | 24 months                                  |
| Novoselac et al. <sup>49</sup> (2004)                | Acute myeloid leukemia       | 10 mg/m <sup>2</sup> (every 3 months)             | 120 mg (60 mg/m <sup>2</sup> )                 | 11 months                                  |
| Beaumont et al. <sup>50</sup> (2003)                 | Acute promyelocytic leukemia | Not reported                                      | 120 mg (mitoxantrone)<br>500 mg (methotrexate) | 16 months                                  |
| Nollet et al. <sup>51</sup> (2006)                   | Acute leukemia               | 12 mg/m <sup>2</sup> / month                      | 58.32mg  | 32 months                                  |
| Nollet et al. <sup>51</sup> (2006)                   | Acute leukemia               | 20 mg / month                                     | 160 mg   | 27 months                                  |

NR=not reported

In our initial document, a 4-year cumulative risk of leukemia of 3.9% in breast cancer patients was reported, however, these patients were also receiving other treatments that might have predisposed them to developing leukemias including radiotherapy<sup>4</sup>.

In summary, there seems to be an increased risk of developing acute myeloid leukemia following therapeutic use of mitoxantrone, though the extent of this risk is unknown and the causality impossible to establish with certainty. Although it appears to be quite low (0.16%) in the relatively short follow-up studies reported above, there is evidence that the disease may develop years after the completion of the treatment, and the overall risk for long-term survivors of MS is almost certainly higher. For this reason it has been recommended that patients be followed for several years after the end of treatment with mitoxantrone in order to determine the true long-term risk of therapy-related leukemia<sup>1 42 58</sup>.

### **New mitoxantrone treatment strategies**

The use of a lower dose of mitoxantrone (5 mg/m<sup>2</sup>) either from the beginning of the treatment or after an induction phase using 12 mg/m<sup>2</sup> has been proposed in order to decrease the risk of toxicity with the drug<sup>56 37</sup>. Other authors proposed a combination of mitoxantrone at regular or low dose and other treatments such as interferonβ-1b<sup>65</sup> or methylprednisolone<sup>35</sup>. Despite the use of lower doses, Ostberg et al. has reported the decrease of LVEF to below 50% in 4 out of 31 patients (13%)<sup>37</sup>. Therefore, the efficacy and safety of these strategies still needs to be confirmed.

### **LOCAL EXPERIENCE AT THE MUHC**

A treatment program with mitoxantrone in patients with multiple sclerosis was developed at the Montreal Neurological Hospital (MNH) of the MUHC in July 2002.

The protocol used prescribes that a dose of 12mg/m<sup>2</sup> of mitoxantrone be administered once a month for the first 3 months and every 3 months thereafter (maximum of 110 mg/m<sup>2</sup>) for SPMS, and 12mg/m<sup>2</sup> monthly for 6 months in patients with RRMS<sup>4</sup>. Details of the treatment protocol can be found in the original TAU report<sup>4</sup>. Patients are monitored for toxicity through blood tests before each mitoxantrone administration, and LVEF through multiple gated acquisition (MUGA) scan at 50, 75, and 100 mg/m<sup>2</sup>, and at 6 months after treatment completion<sup>4</sup>. If a decrease greater than 10% in the LVEF is observed and confirmed by a second evaluation, the treatment with mitoxantrone is discontinued (Dr. Y. Lapierre, personal communication). Decisions about continuation of treatment are made in consultation with the cardiology department of the MUHC and take into account the risks and benefits to the patient of receiving mitoxantrone treatment (Dr. Y. Lapierre, personal communication). As an additional precaution the maximum cumulative dose of mitoxantrone administered at the MUHC MNH has been limited to 110 mg/m<sup>2</sup>, a dose that is lower than the maximum recommended dose of 140mg/m<sup>2</sup><sup>5</sup>.

The report prepared in 2004 by Dr. J. Stewart showed a 16% (8 out of 50) rate of treatment discontinuation as a result of significant side effects of mitoxantrone<sup>14</sup>. These consisted of

extreme fatigue (6%), elevated liver enzymes (4%), changes from baseline LVEF (4%), and heart palpitations (2%)<sup>14</sup>.

Between July 2001 and August 2005, approximately 70 patients, (approximately 18/year) have started treatment with mitoxantrone at the MUHC for aggressive multiple sclerosis.

**Hospital chart review – Results**

In order to estimate the number of patients who had a drop in LVEF or who interrupted the treatment due to other drug toxicities, we have reviewed the treatment records of patients who were treated with mitoxantrone at the MS clinic and whose treatment started before July 2005 as this would allow enough time for two LVEF exams to be performed (as per the MUHC protocol). Fifty-five patient charts were reviewed as they met the eligibility criteria above and were available for review.

Table 4 summarizes the characteristics of these 55 patients.

Table 4 – Patient characteristics

| Patient characteristics (N=55)               | n (%)                             |
|--|-----------------------------------|
| Females                                      | 31 (56%)                          |
| Age, mean (range)                            | 42 years (26 – 52)                |
| Diagnosis                                    | SPMS: 59%                         |
|  | RRMS: 24%                         |
|  | PRMS: 11%                         |
|  | PPMS: 6.5%                        |
| Cumulative dose, mean (range)                | 78.9 mg/m <sup>2</sup> (12 – 108) |
| Time on treatment, mean (standard deviation) | 12 months (7.2)                   |
| Follow-up*, mean (standard deviation)        | 13.6 months (8.1)                 |

\*from start of treatment until latest dose or latest post-treatment LVEF exam in patients who completed or interrupted the treatment

Figure 1 shows the patients’ treatment status.

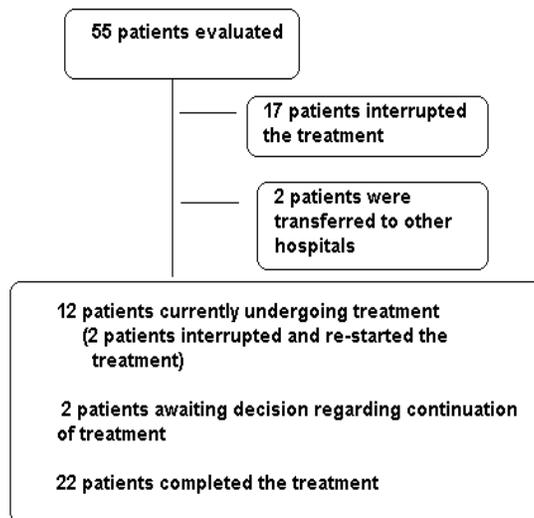


Figure 1 – Flow chart of patient treatment status

In most cases, the cardiotoxicity monitoring (LVEF measurement) was done during the mitoxantrone treatment.

### ***Treatment interruptions***

A total of 19 (34.5%) patients interrupted the treatment (including 2 patients who interrupted and subsequently re-started the treatment):

- 16 patients interrupted the treatment and did not re-start it.
- 2 patients interrupted the treatment, re-started it and are still undergoing treatment with mitoxantrone.
- 1 patient interrupted the treatment with mitoxantrone due to a drop in LVEF, re-started the treatment after recovery, and had to interrupt the treatment again for the same reason.

Table 4 shows the reasons for treatment interruption.

Table 4 – Reasons for interruption

| Reason for treatment interruption | N (%)   | Comments  |
|-----------------------------------|---|---|
| Drop in LVEF to below 50%,        | 7 (12.7%)   | In one of these patients, the LVEF may have already been low at the start of the treatment. |
| Patient request                   | 9 (16.4%)<br>(fatigue:3, nausea: 2, not feeling well: 2, worries about cardiac side-effects: 2) | -   |
| Depressed liver function test     | 2 (3.6%)  | The liver function tests returned to normal after the treatment was interrupted             |
| Low white blood cell count        | 1 (1.8%)  | Recovery status not available   |
| <b>Total</b>                      | <b>19 (34.5%)</b>   |   |

### Cardiotoxicity

Thirteen patients (23.6%) experienced a decrease in LVEF as defined by either a drop to below 50% or an absolute drop of 10% from baseline. In nine patients (16.4%) there was a drop in LVEF to below 50%, 12 patients (21.8%) had a 10% decrease in the LVEF (eight patients had both a decrease to below 50% and a 10% decrease in LVEF). Seven patients permanently interrupted therapy due to this side effect.

Table 5 – LVEF recovery status among the patients with a LVEF drop

| Recovery status      | N (%)   |
|----------------------|---|
|                      | <b>Time of follow-up LVEF measurement</b>   |
| <b>Recovered</b>     | <b>9 (69%)</b><br>Mitoxantrone treatment was re-started in <b>4 patients</b> , 3 did not experience a further LVEF decrease after 24-36 mg/m <sup>2</sup> , and 1 had a second LVEF drop after 12mg/m <sup>2</sup><br><b>2 patients</b> : LVEF recovered despite continuation of treatment<br><b>3 patients</b> : LVEF recovered as measured 1 - 4 months after the mitoxantrone treatment was stopped. |
| <b>Not recovered</b> | <b>2 (15.4%)</b>  |
| <b>Not available</b> | <b>2 (15.4%)</b>  |

The drop in LVEF occurred at a cumulative mitoxantrone dose of 48 mg/m<sup>2</sup> in nine patients (69%), 72mg/m<sup>2</sup> in one patient (7.7%), 96 mg/m<sup>2</sup> in 1 patient (7.7%), and at 108 mg/m<sup>2</sup> in two patients (15.4%). The mean cumulative dose at which the LVEF dropped was 62.8 mg/m<sup>2</sup> (standard deviation (SD): 24.6), and the mean time to LVEF drop was 8.9 months (SD: 6.2). Figure 2 shows the graph of the time to LVEF drop in the 55 patients evaluated.

This illustrates that approximately 25% of patients will experience evidence of left ventricular dysfunction studied with non-invasive cardiac evaluation.

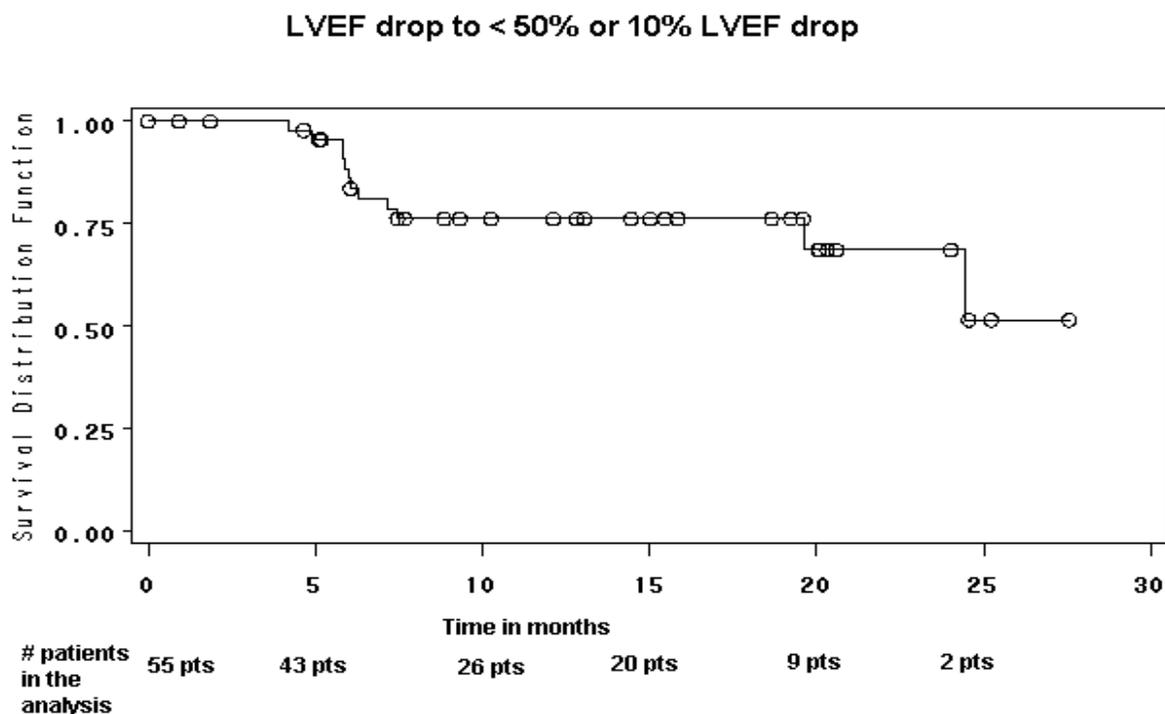


Figure 2 – Time to LVEF drop. Each drop in the “survival” curve indicates a drop in LVEF. The circles indicate censoring, i.e., end of follow-up for patients who did not experience a LVEF drop. Pts = patients  
 Mean follow-up time: 19 months

No cases of congestive heart failure have been identified up to this point.

We did not find any evidence of prior cyclophosphamide or other cardiotoxic drug use among the patients reviewed.

***Leukemia***

One patient (1.8%) died of promyeloid leukemia that may have been induced by the treatment with mitoxantrone (Dr. Y. Lapierre, personal communication).

### ***Other toxicities***

Two patients (4%) needed a decrease in the mitoxantrone dose administered in each cycle from 12 mg/m<sup>2</sup> to 9 mg/m<sup>2</sup> due to slow white blood cells (WBC) count recovery.

One patient (2%) had to interrupt the treatment due to lack of WBC recovery between doses. The recovery status of this patient is still being investigated.

Two patients (4%) needed to interrupt the mitoxantrone treatment due to liver toxicity. The liver enzymes returned to normal after treatment interruption.

### **Costs**

The mitoxantrone treatment protocol used at the MNH remains unchanged since the last report, and therefore, the average cost to the MUHC per patient treated (excluding any possible costs of treatment of complications of mitoxantrone therapy) is expected to be as calculated in the original report, i.e., \$5,000, with a total of \$100,000 if 20 patients receive treatment<sup>4</sup>.

## **SUMMARY**

### **Efficacy**

Since the publication of the previous report three publications have reported evidence of efficacy of mitoxantrone when used in patients with more aggressive forms of MS<sup>21 22 23</sup>. However, in MS patients in general, there is no new evidence of efficacy, and there is still no follow-up longer than 3 years. Thus the previous conclusion that for such cases there is evidence of a small beneficial effect of mitoxantrone, but that the duration of this benefit is still unknown requires no modification. The short follow-up and lack of a comparator group prevents any efficacy conclusions to be drawn from our local chart review.

### **Toxicity**

**Myocardial damage.** There is additional evidence both from the medical literature and from our local assessment that mitoxantrone used for the treatment of MS carries a significant risk of myocardial damage as evidenced by a reduction in left ventricular ejection fraction. Published reports suggest an overall risk, even with moderate dosage, of 3.8% (range 0 –

17.8%), while local experience suggests that with careful and repeated monitoring of LVEF the risk might be 25%. The risk of cardiotoxicity increases with increasing dose but cases have been reported at dosage levels well below the recommended upper limit of 140 mg/m<sup>2</sup>. The long-term cardiac effects are largely unknown. In 9 out of 13 locally observed cases in which LVEF became depressed, this occurred at an accumulated dose below 48 mg/m<sup>2</sup>. The possible adverse effect of previous use of other cardiotoxic drugs such as cyclophosphamide on mitoxantrone cardiotoxicity remains to be proved. Further study of this issue might help physicians to recognize those patients that are at greater risk for this complication. Even on the basis of present evidence, it is clear that patients with prior use of other cardiotoxic drugs or with cardiovascular risk factors should be followed more closely.

Leukemia. Since the last TAU report there have been new reports of acute myeloid leukemia developing months to years after the end of treatment with mitoxantrone for MS. Studies have reported a rate of less than 1% of the disease in patients treated with mitoxantrone for MS but there is reason to believe that longer follow-up, as advocated by some reviewers<sup>1 24,58</sup> will reveal a higher incidence.

### **New treatments for MS.**

Although there are promising research reports, there are as yet no new treatments with greater efficacy or lower toxicity than mitoxantrone available.

### **Local experience**

The staff of the MS clinic of the MNI have kept the flow of patients very close to the limit of 20 per year as recommended in the previous report. No patients in whom this treatment was indicated have yet had to be refused (Y. Lapierre, personal communication).

### **Chart Review**

The approximately 25% rate of drop in LVEF obtained through the MS Clinic chart review is somewhat higher than the highest rate identified in the literature, i.e., Avasarala et al. (5/28, 17.8%)<sup>26</sup>, and much higher than the 3.9% (range: 0 – 17.8%) weighted average rate observed in the literature. This may be due, at least partially, to the use of different criteria

to define LVEF drop and/or different diagnostic methods, i.e., MUGA vs. echocardiography. Congestive heart failure development was not observed among the patients treated at the MUHC. The mitoxantrone cumulative dose in which the LVEF drop was first observed was lower than expected, 48mg/m<sup>2</sup> in 9 out of 11 patients (82%), although Avasarala et al. observed a drop in LVEF at even lower doses, 37mg/m<sup>2</sup> <sup>26</sup>. Thus, there would seem to be virtually no “safe” dose. The patients’ records indicate that the drop in LVEF may be reversible. Nevertheless, longer follow-up is required to determine whether the recovery is sustained, as delayed cardiotoxicity with mitoxantrone has been reported in the literature<sup>30</sup>.

Overall mitoxantrone treatment had to be interrupted in 19 (34.5%) patients. The reasons for interruption were patient request (16.4%), fall in LVEF (12.7%), increased liver enzymes (3.6%), and WBC count drop (1.8%),

## **CONCLUSIONS**

**Since the last report no new evidence indicating more substantial or more permanent benefit of mitoxantrone treatment in a general MS population has been identified.**

**Further evidence of cardiotoxicity even at relatively low doses has been identified. There are also new reports suggesting increased risk of leukemia.**

**Three recent case studies report excellent results of mitoxantrone induction treatment in patients with highly aggressive forms of MS but suffer from a lack of any comparator group.**

**For these reasons the present indications for use use of mitoxantrone in MS should be reconsidered.**

## **RECOMMENDATIONS**

Reports of treatment benefits in aggressive forms of RRMS or SPMS are sufficiently promising to justify its continued study at the MUHC in the context of an observational phase IV data collection to systematically record disease progression and toxic side effects.

Aggressive forms of M. S. are defined as :

1) The occurrence of two relapses, with sequelae, in the 12 months preceding the initiation of mitoxantrone therapy, AND one new gadolinium-enhanced lesion on the MRI in the 3 months preceding the initiation of mitoxantrone therapy whenever possible. (It is recognized that the MRI criterion may not always be applicable at the MUHC).

OR

2) Deterioration of 2 points in the EDSS score in the 12 months preceding the initiation of mitoxantrone therapy, AND 1 new gadolinium enhanced lesion on the MRI in the 3 months preceding the initiation of mitoxantrone therapy.

The rigorous documentation of pre-treatment clinical progression (EDSS change, relapse rates) with gadolinium-enhanced MRI Imaging whenever possible, should be maintained, and continued, during treatment and long-term follow-up so that the experience gained can be eventually added to the knowledge base.

The subsequent use of other cardiotoxic drugs such as cyclophosphamide should be accompanied by cardiac monitoring.

Treatment should only be initiated after full discussion with patients of the limited and uncertain benefits to be expected, the absence of knowledge of the duration of these effects, and the possibility of serious side effects. It is recommended that signed informed consent be obtained.

**It is suggested that the contents of this report be shared with referring physicians with the objective of discouraging mitoxantrone therapy except for those cases most likely to benefit. The MUHC should not authorize any increase in patients above the present threshold of 20 per year.**

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## **APPENDIX 1 SUMMARY AND RECOMMENDATIONS OF THE TAU REPORT** **APPROVED IN DECEMBER 2002**

### **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.

## **Appendix 2 – Observational studies of mitoxantrone in patients with aggressive forms of multiple sclerosis**

### Le Page et al.

An observational study evaluated 100 consecutive patients with an aggressive relapsing remittent form of MS who were treated with mitoxantrone induction treatment between September 1992 and September 2001<sup>21</sup>. The induction treatment consisted of monthly administrations of 12mg/m<sup>2</sup> of mitoxantrone for 6 months<sup>21</sup>. The patients were followed-up for at least one year (maximum 8 years median: 3.8 years), however, the number of patients with follow-up at 2, 3, 4 and 5 years were: 81, 66, 47, and 30 respectively<sup>21</sup>. The patients were evaluated clinically every six months, LVEF was measured by echocardiogram before the treatment, at the end of the induction period and annually thereafter for five years<sup>21</sup>. Magnetic resonance imaging (MRI) was performed at each hospital at different intervals depending on each neurologist's request and also with different machines that may exhibit different potency and imaging parameters<sup>21</sup>. The data was collected prospectively<sup>21</sup> and not in a blinded fashion. In the year prior to the start of the mitoxantrone treatment, 66% of the patients had not received any MS treatment, while among the remaining 34% of the patients, 18% had been treated with interferon beta, 13% with azathioprine, 3% had been treated with methotrexate, immunoglobulines or cyclophosphamide<sup>21</sup>.

After the induction period, the continuation of treatment was left to the discretion of each neurologist and 21 out of 100 patients continued to be treated with mitoxantrone for an additional 2-7 administrations to a maximum cumulative dose of 156 mg/m<sup>2</sup><sup>21</sup>. Other patients either did not receive any treatment, or were treated with interferon beta, azathioprine, methotrexate or glatiramer acetate<sup>21</sup>.

The induction treatment with mitoxantrone was evaluated during the first year and compared with the patient status in the year prior to the mitoxantrone treatment<sup>21</sup>. The annual relapse rate in the year prior to the mitoxantrone induction treatment was 3.20, and it decreased to 0.30 during the first year of treatment ( $p < 0.00001$ ), which corresponded to a 91% decrease in the frequency of relapses<sup>21</sup>. There was a 1.2 decrease in the median EDSS score between baseline and 1 year ( $p < 0.00001$ )<sup>21</sup>. The proportion of patients showing a deterioration in the year prior to the induction treatment was 87%, and it decreased to 4% at the end of the first year ( $p < 0.000001$ )<sup>21</sup>. The proportion of patients with gadolinium-enhanced lesions on MRI decreased from 84% before mitoxantrone to 9% at one year after the treatment started<sup>21</sup>.

According to the authors, at the end of the five years of follow-up, some of the early benefits observed were maintained such as reduced frequency of relapses<sup>21</sup>. The improvement in EDSS score was maintained until the 4<sup>th</sup> year and the percentage of patients not experiencing deterioration was 89% at 2 years, and 79% at 3 years<sup>21</sup>. However, the 4-5-year analyses should be cautiously interpreted as only a fraction of the patients had a long follow-up, i.e., 47% and 30% at 4 and 5 years respectively, which may have resulted in a selected sample of patients that may differ from the original cohort.

Fifteen patients evolved into secondary progressive disease at a median of 2 years after the first administration of mitoxantrone, 3-15 years after the onset of MS<sup>21</sup>.

The study presents a long-term follow-up in a specific group of patients with a more active form of the disease<sup>21</sup>, however, not all patients were followed for more than 1-2 years, and patients received other MS therapies after the induction treatment with mitoxantrone, which does not permit an evaluation of the long-term effect of this individual drug but rather provides information on a sequence of treatments.

#### Correale et al.

One observational study included 10 patients who met the criteria for aggressive form of RRMS while receiving treatment with interferon beta, i.e., at least 3 relapses and an increase in at least one point in the EDSS scale in the 6 months preceding the initiation of mitoxantrone treatment<sup>22</sup>. The patients received induction treatment with mitoxantrone 12mg/m<sup>2</sup> and methylprednisolone 1000 mg monthly for 3 months followed by treatment with interferon beta<sup>22</sup>. There was a decrease in the number of relapses and new Gd-enhanced lesions on MRI measured after the mitoxantrone induction treatment compared to the value in the preceding 6 months<sup>22</sup>. The number of Gd-enhanced lesions on MRI was 7± 1.9 before treatment, 0.5 ±0.7 immediately after mitoxantrone treatment (p=0.002), and 2.7 ±3.9 6 months after the end of mitoxantrone treatment<sup>22</sup>. The number of relapses decreased from 3.2 ±0.4 before treatment to 0.9 ±1.3 1-6 months after the end of mitoxantrone treatment (p=0.004)<sup>22</sup>. The EDSS remained stable during the mitoxantrone induction treatment, 3.4 ± 0.7<sup>22</sup>. The EDSS had been worsening before the start of mitoxantrone treatment, i.e., 2.2 ±0.9 to 3.4 ±0.7<sup>22</sup>.

After the mitoxantrone induction treatment, the patients were treated with interferon beta for 9 months<sup>22</sup>. During this period 7 (70%) patients were considered responders and 3 (30%) patients were considered non-responders based on the relapse rate, presence of new Gd-enhanced lesions on MRI and changes in the EDSS score<sup>22</sup>.

The number of relapses ( $0.4 \pm 0.5$ ), Gd-enhanced lesions on MRI ( $0.16 \pm 0.4$ ), and EDSS scores ( $3.0 \pm 0.8$ ) 24 months after the end of the induction treatment did not differ significantly from the values observed during induction treatment in the seven patients considered as interferon-beta responders<sup>22</sup>. The responders received 15-18 months of interferon-beta treatment<sup>22</sup>. The three non-responders experienced a worsening during interferon-beta therapy, i.e., relapse rates increased from 0 after mitoxantrone treatment to  $2.7 \pm 0.6$  during interferon-beta treatment, EDSS worsened from  $3.4 \pm 0.7$  to  $5.3 \pm 0.3$ , and the number of Gd-enhanced lesions increased from  $0.5 \pm 0.7$  to  $3.3 \pm 1.1$  during the same periods<sup>22</sup>. Mitoxantrone treatment was re-started in these patients at 3-month intervals and after an additional 15-18 months of follow-up, the EDSS was stabilized ( $5 \pm 0.5$ ) and no new relapses or new Gd-enhanced lesions were observed<sup>22</sup>.