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# Ten-year follow up after mitoxantrone induction for early highly active relapsing-remitting multiple sclerosis: an observational study of 100 consecutive patients

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## **ABSTRACT**

**Background:** Six monthly courses of mitoxantrone were approved in France in 2003 for patients with highly active multiple sclerosis (MS).

**Objective:** To report the 10-year clinical follow up and safety of mitoxantrone as an induction drug followed by maintenance therapy in patients with early highly active relapsing–remitting MS (RRMS) and an Expanded Disability Status Scale (EDSS) score < 4, 12 months prior to mitoxantrone initiation.

**Methods:** 100 consecutive patients with highly active RRMS from the Rennes EDMUS database received monthly mitoxantrone 20mg combined with methylprednisolone 1g for 3 (n=75) or 6 months (n=25) followed by first-line disease-modifying drug (DMD). The 10-year clinical impact was studied through clinical activity, DMD exposure, and adverse events.

**Results:** 24% were relapse-free over 10 years and the mean annual number of relapses was 0.2 at 10 years. The mean EDSS score remained significantly improved for up to 10 years, changing from 3.5 at mitoxantrone initiation to 2.7 at 10 years. The probability of disability worsening and improvement from mitoxantrone initiation to 10 years were respectively 27% and 58%, and 13% converted to secondary progressive MS. Patients only remained untreated or treated with a first-line maintenance DMD for 6.5 years in average. In our cohort, mitoxantrone was generally safe. No leukemia was observe and six patients developed neoplasms, including 4 solid cancers.

**Conclusion:** Monthly mitoxantrone for 3 or 6 months, followed by maintenance first line treatment, may be an attractive therapeutic option for patients with early highly active RRMS, particularly in low-income countries.

**Keywords:** multiple sclerosis, disease-modifying therapies, mitoxantrone

## INTRODUCTION

Mitoxantrone was approved by the Food and Drug Administration in October 2000 and in several European countries in 2002. In France, it was approved in October 2003 as an induction drug (i.e. monthly infusions for up to 6 months (12mg/m<sup>2</sup>; maximum cumulative dose 72mg/m<sup>2</sup>) for the treatment of highly active relapsing–remitting MS (RRMS).[1, 2] *Highly active RRMS* is a concept that was introduced by the European Medical Agency (EMA) to define the use of second-line therapy in MS, [3] designating either naïve patients with RRMS who have had at least two relapses within the previous 12 months, or first-line treated patients who have had at least one relapse with an active MRI (at least one gadolinium-enhancing (Gd+) lesion or more than nine T2 lesions).

Randomized trials have demonstrated that short-term immunosuppression with mitoxantrone followed by a first-line disease modifying drug (DMD), such as interferon beta or glatiramer acetate, is more effective than either first-line treatment alone [4, 5] or monthly methylprednisolone [1]. An observational study conducted in our MS expert center among 100 consecutive patients with aggressive RRMS followed for at least 5 years showed sustained clinical benefit for up to 5 years, with an acceptable adverse events profile.[6, 7]

To go one step further, the present study investigated the longer-term impact and safety profile of mitoxantrone (i.e., 10-year clinical follow up) after its use as an induction drug in a new cohort of 100 consecutive patients with early highly active RRMS, as defined by the EMA.[3]

## **PATIENTS AND METHODS**

### **Study population**

We enrolled the 100 consecutive patients with RRMS who had most recently been added to the Rennes European Database for Multiple Sclerosis (EDMUS; 5774 patients with MS),[8] in order to form a cohort of patients with highly active RRMS as defined by EMA for the use of second-line immunosuppressive treatment in MS.[3] These patients were followed for at least 10 years after their first course of mitoxantrone (administered between 2000 and 2009). Patients with a sustained Expanded Disability Status Scale (EDSS) score equal to or above 4, 12 months before starting mitoxantrone [9] were excluded, to avoid the inclusion of patients with potential secondary progressive MS[10]. A flowchart is available in Table S1.

### **Data statement**

Data were collected prospectively, anonymized and entered in the European Database for Multiple Sclerosis (EDMUS) system [8]. The French National Commission for Data Protection and Liberties approved this data collection (CNIL n° 8493536 and 8493536 bis), and confidentiality and safety were ensured in accordance with their recommendations. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

### **Exposure**

Patients received three or six courses of mitoxantrone 20mg IV and methylprednisolone IV 1g, administered at monthly intervals. Although all post-mitoxantrone treatments were described, immediate maintenance therapy referred to treatment initiated within 180 days of the completion of the mitoxantrone courses.

### **Variables**

Demographic characteristics, pre-mitoxantrone relapse, Gd+ lesions, and EDSS scores were collected at baseline. A *relapse* was defined as the occurrence of new isolated neurological symptoms or the worsening of symptoms that had occurred previously, lasting at least 24 hours.[11] The annualized relapse rate (ARR) was computed for the period between M-12 and M0 (i.e. year before

mitoxantrone initiation) and for each of the 10 years following mitoxantrone treatment. MRI data were reported using a binary variable (presence or absence of Gd+ lesions). Two MRIs were considered: the one performed in the year preceding the treatment, and the first post-mitoxantrone MRI, that is, after a median interval of 1.5 months after the final mitoxantrone course ((interquartile range, IQR = 1.1-10.2). Residual EDSS scores were collected outside of relapses: (1) EDSS measured in the year before mitoxantrone initiation (*M-12 EDSS*), (2) EDSS measured 3 months before mitoxantrone initiation (*MO EDSS*), and (3) EDSS measured at the end of mitoxantrone treatment (*post-mitoxantrone*). Disability level was also measured for each of the 10 years of post-mitoxantrone follow up.

## **Outcomes**

### MS activity

Within 10 years of mitoxantrone treatment, we analyzed the number of relapses, ARR, disability level, time to first relapse from first course of mitoxantrone, and time to first EDSS worsening from last course of mitoxantrone. EDSS worsening was defined as follows: an increase of 1.5 points in EDSS if post-mitoxantrone EDSS was 0, an increase of 1 point if post-mitoxantrone EDSS ranged from 1.0 to 5.5, or an increase of 0.5 point if post-mitoxantrone EDSS was above 5.5.

### Treatment exposure

Treatment exposure within 10 years after the end of mitoxantrone was described as follows: for 3-monthly periods during the first year (i.e. 0-3 months, 3-6 months, 6-12 months), then on a yearly basis across the 10 years of follow up. In addition, we recorded the time before receiving first-line treatment from the last course of mitoxantrone and the time before receiving second- or third-line treatment from the last course of mitoxantrone.

### Safety

We recorded short- and long-term adverse events (i.e. during mitoxantrone courses and up to 10 years later).

## **Statistics**

We collected demographic characteristics and MS activity parameters, together with details of treatment exposure over 10 years. We compared the number of relapses during the year before mitoxantrone (M-12 to M0) with the number of relapses each subsequent year, using paired Student test. Likewise, yearly EDSS scores were compared with both M0 EDSS and post-mitoxantrone EDSS. Time to each outcome of interest was studied using Kaplan-Meier estimates. To describe the outcome in each group, we computed the restricted mean survival time (RMST) at 2, 5 and 10 years.[12] The RMST corresponds to the restricted mean time before reaching the outcome. The difference in RMST between two groups might indicate the gain/loss of life before reaching the outcome. Groups were defined according to their therapeutic regimens. Baseline characteristics were compared using the Fisher test. The level of significance was set at 5%. Statistical analysis was performed using R 3.4 software.

## RESULTS

### Study cohort

The 100 consecutive patients with highly active RRMS (78 females and 22 males) received their first course of mitoxantrone at a median age of 29 years (IQR = 23-36), 3.2 years (IQR = 0.7-4.9) after MS onset (Table 1). Between M-12 and M0, 76% of patients worsened by more than 1 EDSS point: mean EDSS change = 2.3 (SD = 2.0); median number of relapses = 3 (IQR = 2-4), and 75 patients had active MRI with at least one Gd+ lesion. The median cumulative dose during the first mitoxantrone exposure was 60 mg/m<sup>2</sup> (IQR = 60-72.5). No patient was lost to follow up (more details in table 1). Prior to the mitoxantrone treatment, 43 patients were treatment naïve (treatment naïve group), whereas 50 have received a first-line treatment (42 with interferon beta, 2 with glatiramer acetate, 5 with both, 1 with teriflunomide) and a further seven had received azathioprine (previously treated group). **Treatment exposure within 10 years after end of mitoxantrone**

After three (75 patients) or six (25 patients) courses of mitoxantrone, the RMST from the last course of mitoxantrone to the start of a new treatment was 3.7 months (95% Confidence Interval, 95%CI



[3.3, 4.1]). Post-mitoxantrone treatment was either first-line treatment (interferon beta, glatiramer acetate, teriflunomide, dimethylfumarate), second-line treatment (fingolimod, natalizumab), or third-line treatment (mitoxantrone, alemtuzumab). Among the 87 patients with immediate maintenance therapy, 38 received 3-monthly mitoxantrone (median duration: 9.6 months, interquartile range, IQR: 9.0-12.5) , 27 interferon beta, 18 glatiramer acetate, and four received an off-label treatment (2 low oral dose of 100mg cyclophosphamide per week and two 2g/d oral mycophenolate mofetil). Figure 1 indicates that most patients either went on to receive a first-line treatment after mitoxantrone (54% at Year 2, 59% at Year 5, and 40% at Year 10) or remained untreated (22% at Year 2, 17% at Year 5, and 24% at Year 10). The use of 3-monthly mitoxantrone decreased over time, as a result of cumulative experience with the use of mitoxantrone, the increase availability of MRI exams in routine practice, and the new approved DMDs. Comparisons of data on maintenance therapy status are available in Tables S2 and S3.

The probability of receiving a second- or third-line treatment, excluding the 3-monthly mitoxantrone, was 11% (95% CI [5%, 17%]) at 5 years and 42% (95% CI [32%, 51%]) at 10 years. After the first course of mitoxantrone, 58 patients received a second- or third-line treatment, excluding the 3-monthly mitoxantrone, within a RMST of 6.5 years (95% CI [5.8, 7.2]). Patients who had been treated before mitoxantrone received a new second- or third-line treatment 2 years sooner than treatment naive patients (-1.9 years [-3.2, -0.7]).

### **Early impact on clinical MS activity**

Mean ARR decreased significantly from 2.8 (M-12 to M0) to 0.40 during the first year of follow up ( $p < 10^{-4}$ ), with 74% of patients remaining relapse-free (figure 2). Mean EDSS improved significantly by 1.3 points, decreasing from 3.5 at M0 to 2.2 at Year 1 ( $p < 10^{-4}$ ), with an improvement in EDSS scores for 67% of patients as early as the end of mitoxantrone (mean EDSS post-mitoxantrone: 2.3). The post-mitoxantrone control MRI showed no Gd+ lesions for 82 (85%) of the 96 patients whose scans were analyzed.

### **Long-term impact on clinical MS activity over 10 years following mitoxantrone**

As shown in Figure 2A, the significant reduction in relapse frequency was maintained for up to 10 years. At 10 years, the annual proportion of relapse-free patients was 83% (mean ARR=0.2), and 24 patients had had no relapse since the mitoxantrone courses (i.e. for 10 consecutive years). RMST to the first relapse after mitoxantrone initiation was 3.9 years (95% CI [3.3, 4.7]). As shown in Figure 2B, compared with M0, the mean EDSS score remained significantly improved for up to 10 years. The percentage of *nonworsening* patients across the 10 years following mitoxantrone initiation were 82% at 5 years and 73% at 10 years. The probability of disability worsening and improvement from mitoxantrone initiation to 10 years were respectively 27% and 58%. From the post-mitoxantrone EDSS, RMST to first EDSS worsening after the last course of mitoxantrone was 8.2 years (95% CI [7.6, 8.8]), with a probability of worsening of 35% [25%, 44%] at 10 years. In addition, the probability of converting to secondary progressive MS was 13% [6%, 20%].

### **Group comparisons**

As shown in Table 1, previously treated patients had a more advanced disease than treatment-naive patients (longer MS duration, higher number of relapses, more disabled, and greater MRI activity). Figures 3 and 4 show RMST from the first course of mitoxantrone to the first relapse, and from the last course of mitoxantrone to the first EDSS worsening. Over 10 years, RMST to first relapse was significantly longer (2 years) for treatment-naive patients than for previously treated patients (Figure 3.A). Over 2 years, and 5 years, the time to first relapse was significantly longer for patients treated

by 3-monthly mitoxantrone after the initial courses in comparison with patient treated by an immunomodulatory treatment (Figure 3.B). Over 5 years, being treated with a maintenance therapy within 3-6 months after the end of mitoxantrone delayed the first relapse (difference of 1 year [0.1, 1.9]). This effect was stronger over 10 years (difference of 2 years [0.4, 3.6]) (Figure 3C). Regarding first EDSS worsening no difference was found when we compared the therapeutic regimen groups (Figure 4).

### **Safety**

Table 2 summarizes the side effects during mitoxantrone treatment and over 10 years. Long-term side effects were described according to their link to mitoxantrone. During mitoxantrone exposure, asthenia (40%) and nausea or vomiting (32%) were the most frequent side effects. Over the long term, six patients developed benign or malign neoplasms (4 with solid cancers). No link with mitoxantrone was identified, but as we could not exclude concerns about an increased risk of developing cancer, we categorized the link as unknown. No leukemia was observed. Two patients had a low left ventricular ejection fraction (< 50%): one transitory at 1 year post-mitoxantrone, and one sustained up to the 10-year follow up, observed after a second mitoxantrone exposure. One patient developed septal hypokinesia. Among the 78 women, seven had transitory amenorrhea (9%; median age at mitoxantrone initiation: 34 years) and three persistent amenorrhea (4%; median age at mitoxantrone initiation: 37 years). Over 10 years, 31 women started a pregnancy, resulting in 38 live births, all in good health, three spontaneous abortions, one ectopic pregnancy, and three induced abortions: one being on natalizumab, one owing to trisomy 21, and one owing to severe disease requiring mitoxantrone treatment (third period of mitoxantrone exposure).

Overall, three patients died, at 2, 3 and 5 years after mitoxantrone initiation. For two patients, who died at 2 and 3 years, aged 48 and 33 years, the death was related to the severity of the disease (both had an EDSS score of 7 before death). The last observed death, at 5 years, was due to a myocardial infarction, unrelated to mitoxantrone, as the coronary disease and severe atherosclerosis were attributed to smoking and alcohol abuse.

## DISCUSSION

In this cohort of MS patients with early and very active relapsing disease, treated with mitoxantrone as an induction drug followed by a maintenance therapy, we observed at 10 years that one quarter of patients were relapse-free since the mitoxantrone courses, the mean annual number of relapses was 0.2 and the mean EDSS score remained significantly improved for up to 10 years. In addition, 73% did not worsen after mitoxantrone initiation. The limited population size, especially for subgroup analyses, probably limits the significance of some results. We enrolled a cohort of patients with highly active RRMS, as defined by EMA for the use of second-line immunosuppressive treatment in MS,[3] for as pointed out by the 2018ECTRIMS workshop group, consensus on the definition of aggressive MS is lacking.[13] Patients with an EDSS score equal to or above 4, 1 year before mitoxantrone treatment, were excluded from the cohort for at least three reasons. First, our epidemiological data [14] indicated that after reaching irreversible EDSS 3, the influence of relapses on disability progression ceases to be clear. A similar observation was made by Scalfari et al,[15] who showed that relapses influence the risk of disability progression or the risk of moving to secondary progressive MS only at the early stage of RRMS (before 3 years). Second, a 5-year observational study,[7] found that patients with RRMS who had an EDSS score equal to or above 4 before starting mitoxantrone were more at risk of disability progression. Third, Lorscheider and colleagues [10] showed that patients with RRMS who had reached EDSS 4 had a high risk of entering the secondary progressive phase of the disease. Patients in our RRMS cohort were good candidates for receiving early intensive immunosuppression, given that their disease was highly active (median relapses: 3; 75% Gd+ at baseline) while still in the early stage (median age: 29 years; median MS duration: 3.2 years).

A previous observational study conducted in the same MS expert center followed 100 patients with aggressive relapsing MS for at least 5 years.[7] There was no overlap in the study periods, such that

no patient participated in both studies. In this 5-year study, over the longer term, the ARR reduction was sustained (0.29-0.42 for up to 5 years), median time to first relapse was 2.8 years, and disability remained improved or stable for up to 5 years. These 5-year published data are in line with the data for the first 5 years of the present 10-year observational study.

To our knowledge, only two studies had previously focused on the effect of mitoxantrone at 10 year. [16, 17] The first study, by Foo and colleagues,[16] included 34 patients with a relapsing form and 19 with a progressive one, and showed a beneficial effect of mitoxantrone regarding relapse activity, with an ARR of 0.3 at 10 years (0.2 in our study) and a mean time to first relapse of 2.3 years (4 years in our study).[16] In the second study, by Chartier and colleagues,[17] included 155 patients with a relapsing form at treatment initiation., the probability of disability worsening was 76% (vs. 35% in our study). These discrepancies were probably due to major differences in patients' baseline characteristics, with patients being older at mitoxantrone initiation (35 vs. 30) and having a longer mean MS duration (7.5 vs. 3.7 years) in their study. Maintenance therapy was introduced later (11 vs. 3 months in our study). An induction strategy (mitoxantrone systematically followed by a maintenance therapy) might have been more relevant, as the comparisons of patients who received first-line therapy 3-6 months after the end of mitoxantrone versus those who were treated after 6 months post-mitoxantrone highlight the importance of earlier maintenance therapy (3-6 months).

Although there were no long term clinical studies specifically devoted to very active RRMS, long term observational studies were performed in active relapsing remitting MS patients treated with natalizumab or fingolimod[18,19]. The 10 years real-world natalizumab study [18], including 6148 patients (age at natalizumab initiation: 37) showed a probability of disability worsening at 10 years of 28% (27% in our study). Likewise, the 10 years real world fingolimod study[19], including 4086 patients showed a probability of disability worsening at 10 years of 37% (Table 3). These data suggest that mitoxantrone induction, prior to immunomodulatory treatment might be an alternative to long-term use of natalizumab or fingolimod. Our results support the short-term use of mitoxantrone, followed by a maintenance therapy for patients with early highly active RRMS.

However, the potential toxicity of mitoxantrone must be taken into account, given that the duration and cumulative dose of mitoxantrone treatment (when used as an induction drug) are lower in France (36-72 mg/m<sup>2</sup>) than in other countries (up to 140 mg/ m<sup>2</sup>). In our cohort, mitoxantrone was generally safe: fewer side effects were observed than in previous studies.[6, 7] No death related to mitoxantrone was observed over the 10-year study period. Only half the patients underwent a systematic yearly echocardiogram at 5 years after mitoxantrone (49/98 living patients), thus limiting the completeness of the cardiotoxicity analysis. Regarding cancer, the incidence rate in MS should be estimated taking several criteria (e.g., age) into account, making it difficult to compare our results. Nevertheless, the incidence of solid cancer in our study (4/1000 patient years) was close to the cancer incidence published in RRMS placebo group of two phase 3 trials (10 for 836 patient years in FREEDOMS and 3 for 720 patients years in TEMSO) [20,21]. A previous retrospective cohort study on malignancies after mitoxantrone (N=678 MS patients, median follow-up: 8.7 years) showed a mild increase of incidence in comparison with the general German population (ratio: 1.50 (95%CI: [1.05–2.08]) [22]. In addition, Rivera and colleagues in their prospective 5-year phase IV study (N= 509, mean age at mitoxantrone initiation: 46), reported 3 solid cancers and pointed out the risk of hematological malignancies based on two acute myeloid leukemia and one chronic myeloid leukemia[23]. In addition, neither leukemia nor severe infection was observed in our cohort, even though acute leukemia is a well-known, albeit rare, severe side effect of mitoxantrone.[6,23] In the young female population, persistent amenorrhea was rare, as it was only observed in 4% of patients (aged 30, 37, 43 years) at the start of mitoxantrone treatment.

Although our study benefitted from a high quality of data from medical records, which were reviewed by a neurologist (GLC or CR), the collection of MRI data over time remained fragmented and we were not able to assess accurate MRI data to track changes over 10 years.

## **Conclusion**

In our observational study of 100 consecutively treated patients with early highly active RRMS, monthly mitoxantrone for a short period of 3-6 months, followed by a maintenance therapy with a first-line DMD, resulted in low clinical disease activity and low disability progression for up to 10 years, with an acceptable profile of adverse events. This beneficial effect, associated with its low cost, makes mitoxantrone an attractive therapeutic option for this particular population, especially in low-income countries and suggest that this strategy of early intensive but short term immunosuppression with an induction drug deserves consideration.

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**Table 1: Demographic characteristics and multiple sclerosis activity of the whole study cohort and the previously treated and treatment-naïve groups**

	All	Treatment naïve	Previously treated	Test (Fisher)
<b>Demographics</b>				
<i>N</i>	100	43	57	
Sex (F/M)	78/22	33/10	45/12	0.812
Median age in years at MS onset (IQR <sup>1</sup> )	25 (20-31)	27 (22-33)	24 (20-30)	
Median age in years at mitoxantrone start (IQR <sup>1</sup> )	29 (23-36)	28 (23-34)	30 (24-36)	
< 30 – <i>n</i> (%)	51	23 (53.5%)	28 (49.1%)	0.690
≥ 30 – <i>n</i> (%)	49	20 (46.5%)	29 (50.9%)	
Median MS duration in years at mitoxantrone start (IQR <sup>1</sup> )	3.2 (0.7 - 4.9)	0.5 (0.2- 1.8)	4.2 (3.2-7.8)	
0-3 – <i>n</i> (%)	48	35 (81.4%)	13 (22.8%)	<10 <sup>-4</sup>
3+ – <i>n</i> (%)	52	8 (18.6%)	44 (77.2%)	
<b>MS activity</b>				
<b>Relapses</b>				
Median relapses within 12 months before mitoxantrone therapy (IQR <sup>1</sup> )	3 (2-4)	2 (1-3)	3 (3-4)	
[1; 2] – <i>n</i> (%)	39	26 (60.5%)	13 (22.8%)	10 <sup>-4</sup>
[3; +] – <i>n</i> (%)	61	17 (39.5%)	44 (77.2%)	
<b>Disability</b>				
M-12 median EDSS (IQR <sup>1</sup> )	0 (0-2)	0 (0-0)	2 (1-3)	
M-12 mean EDSS ( <i>SD</i> <sup>§</sup> )	1.1 (1.3)	0.4 (0.9)	1.7 (1.2)	
[0; 2.5] – <i>n</i> (%*)	75 (84%)	40 (95.2%)	35 (74.5%)	0.008
[3; 4] – <i>n</i> (%*)	14 (16%)	2 (4.8%)	12 (25.5%)	
NA	11	1 (-)	10 (-)	
M0 Median EDSS (IQR <sup>1</sup> )	3.5 (2.5-4)	3.5 (2-4)	3.5 (2.9-4)	
M0 Mean EDSS ( <i>SD</i> <sup>§</sup> )	3.5 (1.6)	3.4 (1.5)	3.5 (1.5)	
Mean EDSS change (M0 - M-12) ( <i>SD</i> <sup>§</sup> )	+2.3 (2.0)	-	-	
<b>MRI at baseline</b>				
Number of Gd+ lesions at baseline <sup>b</sup> – <i>n</i> (%)				
0	25	7 (16.3%)	18 (31.6%)	0.028
1	23	7 (16.3%)	16 (28.1%)	
[2; +]	52	29 (67.4%)	23 (40.4%)	
Change in number of T2 lesions <sup>c</sup> compared with MRI within 12 months – <i>n</i> (%)				
Increase	54	12 (27.9%)	42 (73.7%)	<10 <sup>-4</sup>
Stable	17	6 (14%)	11 (19.3%)	
Unavailable	29	25	4	

<sup>1</sup>IQR: interquartile range

<sup>§</sup>SD: standard deviation

\*Computed on available data (i.e. for 89 patients)

<sup>a</sup>EDSS: Expanded Disability Status Scale, <sup>b</sup>Gd+: gadolinium enhancing lesions, <sup>c</sup>T2 lesion: new lesion visible on T2-weighted images, compared with a cranial MRI performed within 12 months before baseline

**Table 2: Summary of study cohort’s mitoxantrone safety profile during mitoxantrone exposure and over 10-year follow up**

	<b>All (N = 100)</b>
<b>During mitoxantrone exposure</b>	
Asthenia	40
Nausea or vomiting	32
Hair loss	18
Minor infectious disease (upper respiratory tract infections, urinary)	15
Epigastralgia	5
Aphtha	2
Diarrhea	2
Headache	2
Faintness (without loss of consciousness)	1
Acute hepatitis	1
Transitory hematocrit increase	1
Rash	1
<b>Over 10-year follow up</b>	
Neoplasms	
Brest cancer: 2	
Ovarian cancer: 1	
Testicular teratoma: 1	<i>Unknown link to mitoxantrone</i>
Atrium myxoma: 1	
Cervical condyloma: 1	
Asymptomatic changes on echocardiogram	<i>Related to mitoxantrone</i>
Premature ovarian insufficiency	<i>Related to mitoxantrone</i>
Gammapathy	<i>Unknown link to mitoxantrone</i>
Myocardial infarction	<i>Unrelated to mitoxantrone</i>

**Table 3: Summary of long-term data of natalizumab and fingolimod study in comparison with our study of mitoxantrone at ten years**

	<b>Study TOP up to 10 years  (natalizumab) 6148 patients  <i>Butzkueven et al, 2020</i></b>	<b>Study LONGTERMS up to 14 years  (fingolimod) 4086 patients  <i>Cohen et al, 2019</i></b>	<b>Our study over 10 years  (mitoxantrone) 100 patients</b>
Age at study drug initiation	37	38	29
Mean disease duration	7.8	8.7	3.2
Number of relapses within 12 months before study drug initiation	2	1.3	3
Mean EDSS at initiation	3.5	2.4	3.5
% naïve patients	15.5%	32%	43%
Mean time on study drug*	3.3 y	4.2 y	6 m
Mean Follow-up (years)	5.2 y	8.6 y	10 y
% of lost-of-follow-up patients	34.4%	14.8%	0%
% study drug discontinuation	27%	64%	0%
ARR over 10 years**	0.15	0.19	0.33
ARR at 10 years**	≤0.20	0.17	0.20
% of relapse free over 10y	45.8%	45.5%	24%
% of 6m disability worsening 0- 10 y	27.8%	37%	27%
% of 6m disability improvement 0- 10 y	23.4%	NA	58%

\*Study drug is either natalizumab, or fingolimod or mitoxantrone, depending on the column,

\*\* Annual Relapse Rate (ARR)

## Figures legends

**Figure 1: Distribution of patients according to their annual treatment exposure over 10 years from first mitoxantrone course**

**Figure 2: Changes in clinical parameters (relapse and disability) of multiple sclerosis activity over 10 years**

**Figure 3: Restricted mean time to first relapse according to therapeutic regimen over 2, 5 and 10 years**

*A: Previously treated patients compared with treatment-naive patients; B: 3-monthly mitoxantrone-treated patients compared with immunomodulatory-treated patients; C: Patients treated within 6 months after end of mitoxantrone compared with patients treated later*

**Figure 4: Restricted mean time to first disability worsening according to therapeutic regimen over 2, 5 and 10 years**

*A: Previously treated patients compared with treatment-naive patients; B: 3-monthly mitoxantrone-treated patients compared with immunomodulatory-treated patients; C: Patients treated within 6 months after end of mitoxantrone compared with patients treated later*

Figure 1 (color)

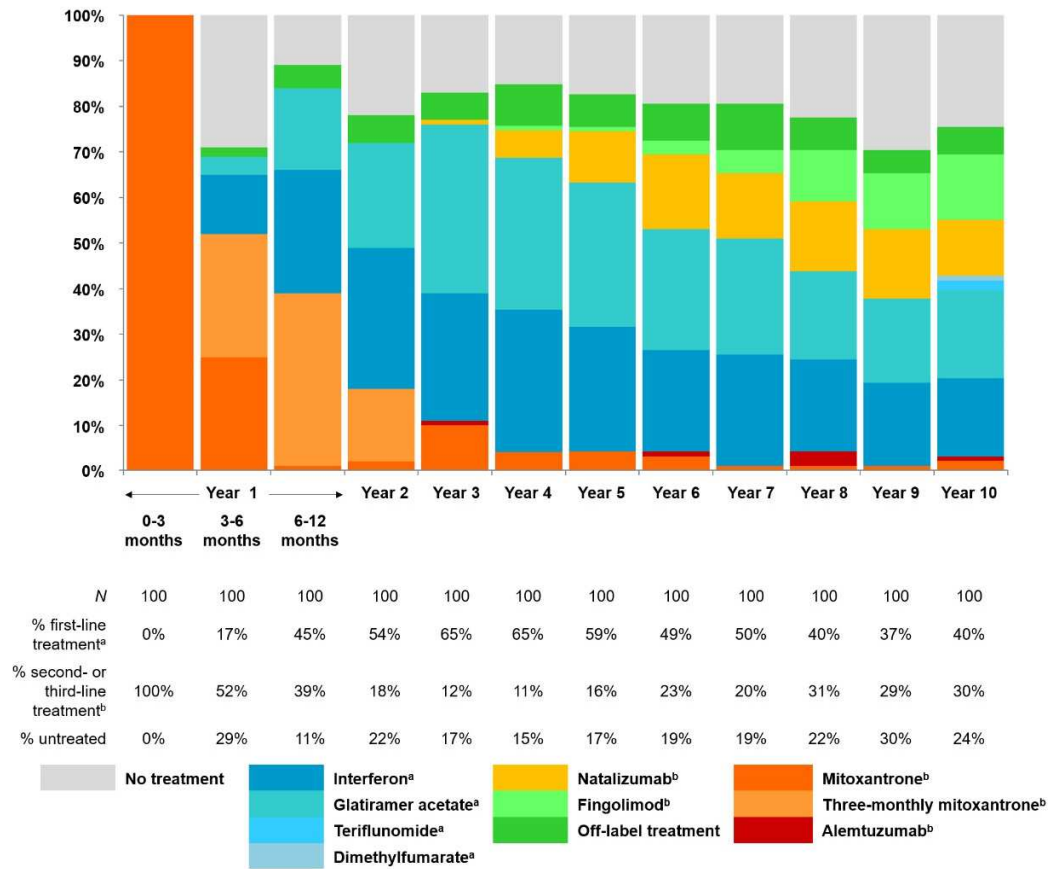
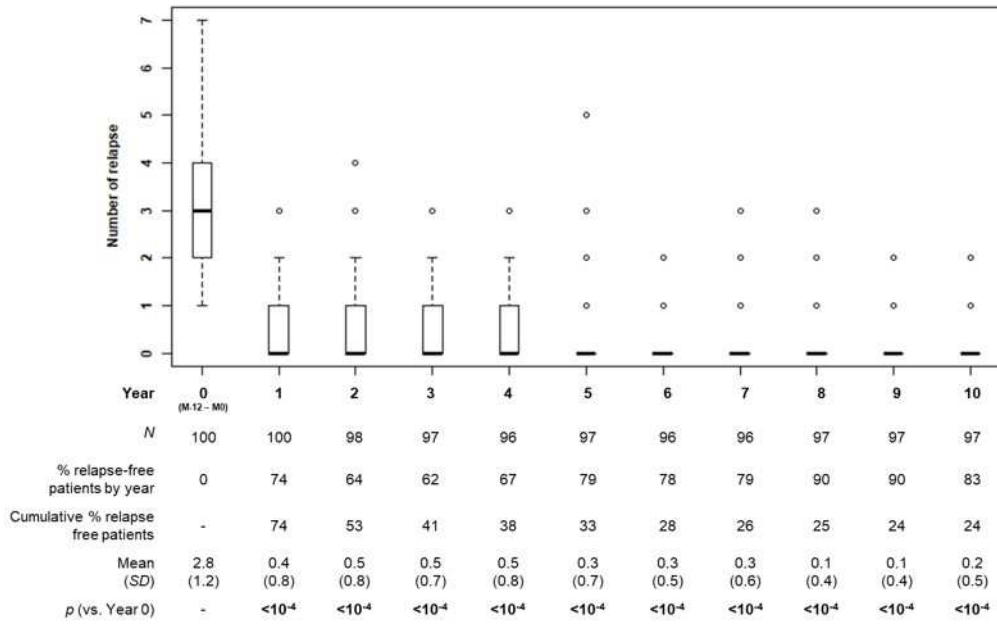




Figure 2

A. Relapse



B. Disability

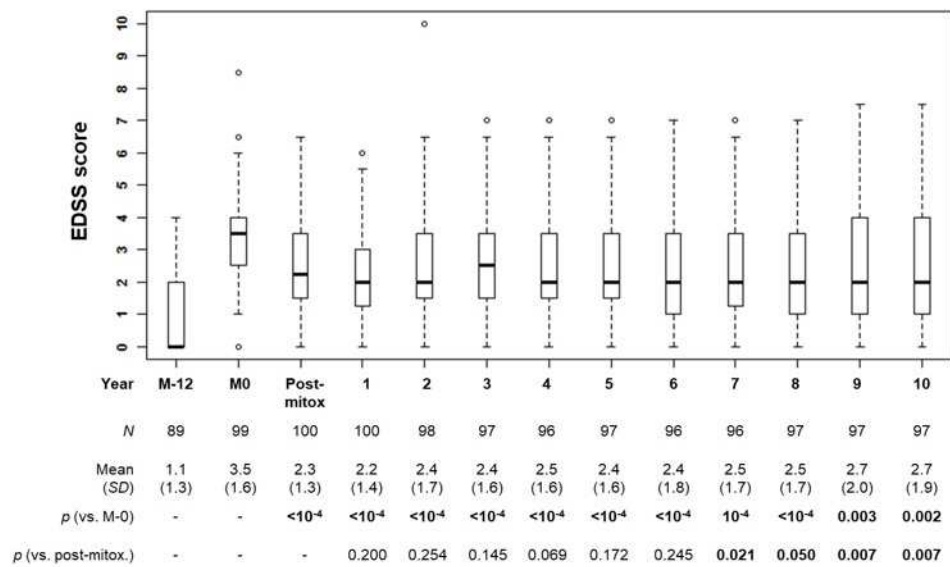
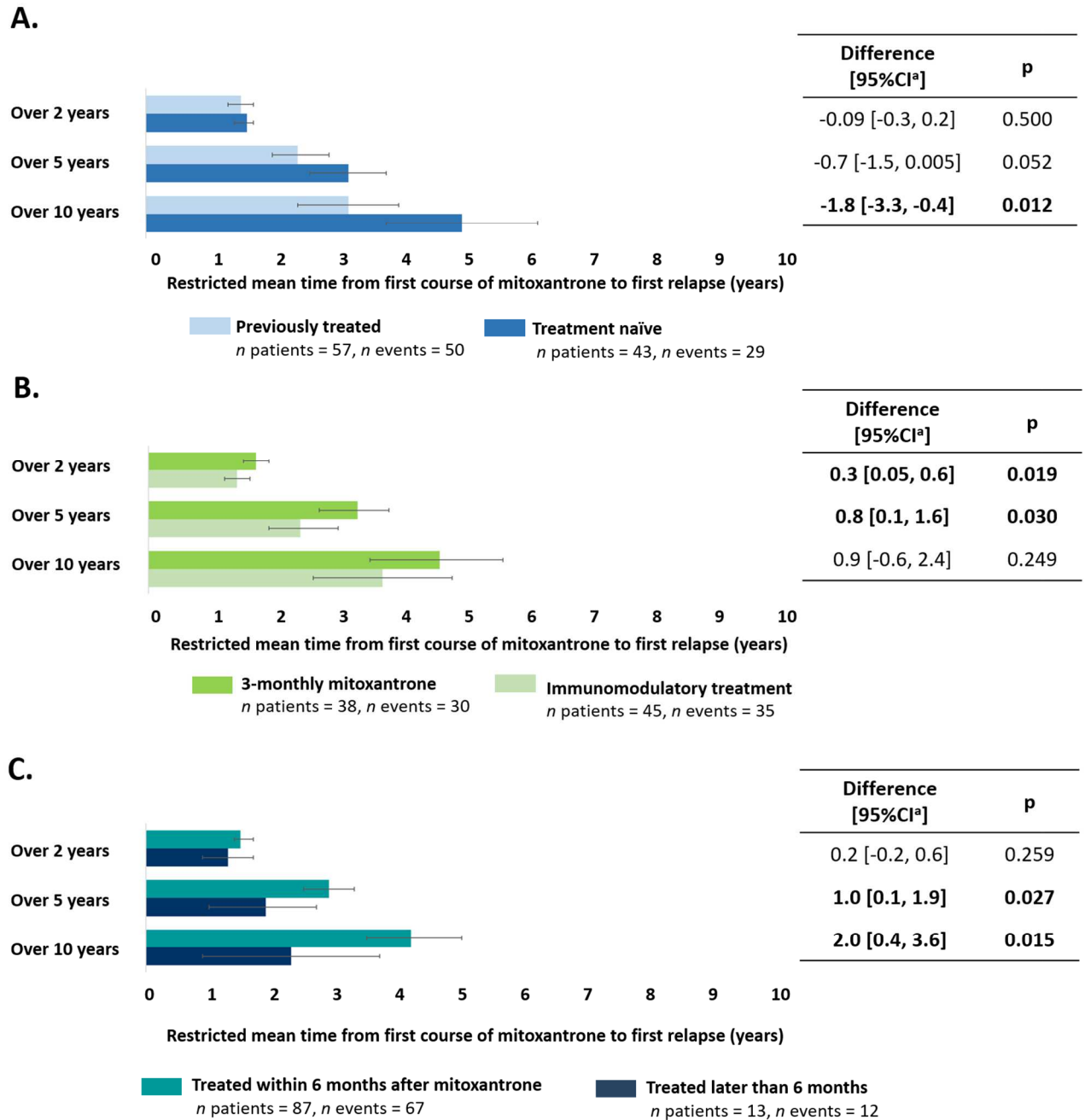
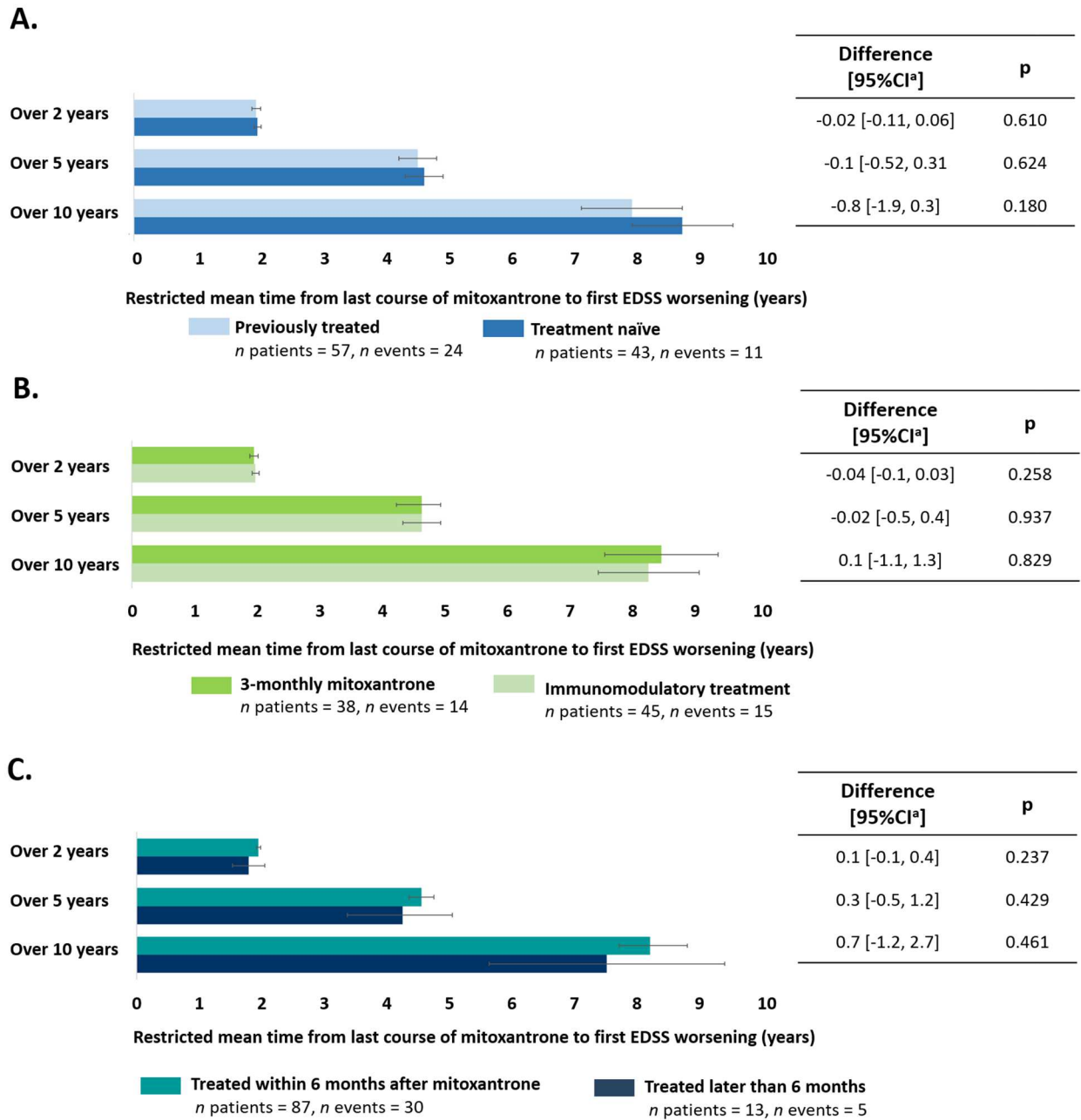


Figure 3 (color)



<sup>a</sup>CI: confidence Interval

Figure 4 (color)



<sup>a</sup>CI: confidence Interval