



Mitoxantrone-Therapy Associated Menstrual Dysfunction in Patients with Multiple Sclerosis

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INTRODUCTION

Mitoxantrone (Novantrone®) is an established, FDA-approved, treatment for patients with secondary-progressive, progressive-relapsing, or worsening relapsing-remitting multiple sclerosis. Its long-term use is limited because of the risk of dose-dependent cardiotoxicity and leukemia. In pre-menopausal women there is an additional concern of ovarian failure; amenorrhea has been noted in clinical trials but has not been thoroughly examined. In order to further evaluate the risk of menstrual dysfunction, we investigated the incidence of menstrual irregularities in a subset of pre-menopausal women treated with mitoxantrone at our center.

DESIGN AND METHODS

Patient Selection:

- 47 pre-menopausal women ranging in age from 18 to 50 were included in the study.
- All women had received two or more mitoxantrone treatments (12mg/m² IV infusion every 3 months) and were menstruating at the time of their first treatment.

Assessment of menstrual function:

- A detailed menstrual history was obtained from each woman. Information was obtained about:
 - Age of menarche, use of oral contraceptives, and number of mitoxantrone treatments.
 - Duration and flow of menstrual cycle prior to, during, and following treatment.
 - Time of onset of menstrual irregularities following initiation of treatment.
 - Menstrual changes post-treatment with follow-up duration of two years.
- All data was subjected to statistical analysis (Fisher's exact test)

Table 1: Patients Characteristics

Patient Demographics	n
Total number of patients	47
Age range	18-50
Number of mitoxantrone treatments	2-9
Patients taking oral contraceptives	8

RESULTS

Table 2: Effect of Treatment on Menses

ID#	Age	Menstrual status on treatment	Outcome after two years	ID#	Age	Menstrual status on treatment	Outcome after two years
01	18	No change	No change	24	41	Immediate change, ↑ flow, ↓ duration	Resolved
02	26	Change after 9 months ↓ flow, ↓ duration	Irregular ↓ flow, ↓ duration	25	41	No change*	No change
03	27	No change*	No change	26	41	No change*	No change
04	28	Change after 1 year ↑ flow, ↓ duration	Resolved	27	41	Immediate change, absent	Absent
05	30	Immediate change ↓ flow, ↓ duration	Resolved	28	41	Change after 2 months, irregular cycle, then absent	Absent
06	31	Immediate change, ↓ duration	Resolved	29	41	Change after 2 months, ↓ flow, ↓ duration	Resolved
07	31	No change*	No change	30	42	Immediate change, ↓ flow, ↓ duration	Irregular, ↓ flow, ↓ duration
08	31	No change	No change	31	42	No change	No change
09	32	No change*	No change	32	42	Change after 2 months, absent	Absent
10	32	Immediate change, absent	Resolved	33	42	Change after 2 months, ↑ flow, then absent	Absent
11	33	No change*	No change	34	42	Immediate change, absent	Resolved
12	34	Change after 3 months, ↑ flow	Resolved	35	43	Immediate change, absent	Absent
13	36	Immediate change, ↓ flow, ↓ duration	Resolved	36	43	Change after 2 months, ↑ flow, ↓ duration, then absent	Absent
14	37	No change	No change	37	44	Immediate change, absent	Absent
15	37	Immediate change ↓ flow, ↓ duration	Irregular, ↓ flow	38	44	Immediate change, absent	Irregular, ↓ flow, ↓ duration
16	38	No change*	No change	39	44	Change after 3 months, absent	Resolved
17	38	Immediate change, absent	Resolved	40	45	Change after 1 year, ↓ flow, ↓ duration, then absent	Absent
18	38	Immediate change, ↓ flow, ↓ duration	Resolved	41	46	Immediate change, absent	Irregular ↓ flow, ↓ duration
19	39	Change after 6 months (duration)	Resolved	42	46	Change after 3 months, ↓ flow	Resolved
20	39	Immediate change, irregular cycle	Resolved	43	46	Change after 9 months, absent	Resolved
21	40	Immediate change, absent	Irregular	44	48	Immediate change, absent	Absent
22	40	Change after 9 months, absent	Absent	45	49	Immediate change, absent	Absent
23	40	Immediate change, absent	Absent for 1 year, then resolved	46	49	Immediate change, absent	Absent
24	40	Immediate change, absent	Resolved	47	50	Immediate change, absent	Absent

* Patients were on birth control during treatment

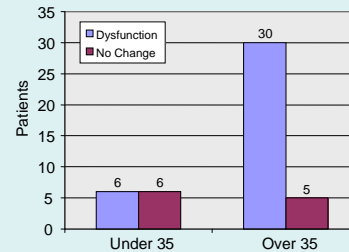
Changes in menstruation:

Thirty-six of the 47 patients (77%) reported changes in their menstrual function while on treatment. Of the 11 who did not experience menstrual dysfunction, 8 were taking oral contraceptives, and the remaining three were under age 40 (ages 18, 31, and 37). Surprisingly, there was no correlation between the number of treatments and the occurrence of menstrual dysfunction [data not shown].

Age and dysfunction:

The frequency of menstrual irregularities while on mitoxantrone correlated with increasing age as shown in figure 1 below. Arbitrarily taking age 35 as a measure, 50% of patients under 35 were affected, whereas above that age, 86% experienced menstrual dysfunction [P=0.0198].

Figure 1: Correlation of age with menstrual dysfunction



Younger women were more likely to have returned to normal menstrual function two years post-treatment. Eleven of the 15 women (73%) ages 40 and below who experienced a change in menstrual status following initiation of treatment later returned to normal. However, of the 21 women over age 40 experiencing a change in menstrual function, only 6 (29%) returned to their prior status following cessation of treatment.

Secondary Ovarian Failure

Following cessation of treatment, secondary ovarian failure, characterized by an absence of menses for 6 months or more, was seen in only 9% of patients below the age of 40. However, above that age, 50% of patients appeared to have mitoxantrone treatment-induced ovarian failure [P<0.05]. Treatment-induced ovarian failure was more strongly correlated with age than with number of treatments, as it was seen in several patients receiving as few as 3 mitoxantrone treatments.

Table 3: Treatment-Induced Ovarian Failure

Age of subjects	40 and below	Over 40
Number of subjects	23	24
Number of subjects with secondary ovarian failure	2	12

CONCLUSIONS

- Menstrual irregularities occur in more than 75% of patients on mitoxantrone therapy and all female patients should be warned of this risk prior to starting treatment.
- Older women are more likely to experience a change in their menstrual cycle following treatment and are also at a higher risk of becoming menopausal.
- Although not investigated in this study, it is possible that fertility is reduced in response to treatment.