Mitoxantrone in secondary progressive multiple sclerosis: a review of toxicity in 41 patients

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Aims: The primary objective of this study was to summarize the toxicity of mitoxantrone treatment of secondary progressive multiple sclerosis (SPMS), with particular focus on cardiotoxicity, hematological and nonhematological toxicities. **Methods:** A total of 41 patients with SPMS were treated with mitoxantrone and their charts retrospectively reviewed for efficacy of treatment and frequency of toxicity. **Results:** Mitoxantrone toxicity was common but treatable, and was effective in achieving disease stabilization in the majority of patients. **Conclusions:** When monitored appropriately, mitoxantrone is safe and effective in the treatment of SPMS.

Mitoxantrone (Novantrone®; Immunex) is an immunosuppressive agent approved for treatment of secondary progressive multiple sclerosis (SPMS). Mitoxantrone has established efficacy in patients with SPMS, yet its usage is limited by toxicities, such as cardiotoxicity and myelosuppression [1,2]. Some authors have found a decline in left-ventricular ejection fraction (LVEF) once a mitoxantrone dosage greater than 100 mg/m^2 is reached [3,4], whereas others have found no cardiotoxicity up to 96 mg/m^2 [5]. Additionally, mitoxantrone, as a cytotoxic agent, has myelosuppressive side effects that may lower the threshold for infection [6,7] and, in rare cases, may increase the risk of treatment-related leukemia [8,9].

The primary objective of this study is to summarize the toxicity of treatment, with particular focus on cardiotoxicity, hematological and nonhematological toxicities.

Patients & methods

The charts of 41 patients were retrospectively reviewed following approval from the university institutional review board (**Table 1**).

All patients met criteria for SPMS [3] and were treated with mitoxantrone (12 mg/m^2) every 3 months. Pre-treatment echocardiograms were obtained, and those with an LVEF greater than 50% were started on mitoxantrone (no screen failures). Echocardiograms were obtained each year and treatment was discontinued if LVEF declined to less than 50%. Complete blood counts (CBCs) were obtained on the day of treatment and 2 weeks after each infusion of mitoxantrone. Grade III or higher neutropenia was treated with cytokines (granulocyte colony-stimulating factor [G-CSF]) and antibiotics, as needed.

Toxicities evaluated included cardiac, hematological and nonhematological, and all were graded using the National Cancer Institute (NCI) common toxicity criteria version 2.0. Total instances of neutropenia were recorded, and only Grades III and IV toxicities were considered clinically relevant.

Results

Three (7%) patients had Grade I (decline of greater than 10% from baseline LVEF) cardiotoxicity, and four (9%) had Grade II (decline of greater than 20% from baseline LVEF) cardiotoxicity. Post-treatment echocardiograms demonstrated normalization of LVEFs in four patients with cardiotoxicity (**Table 2**) and three were lost to follow-up. No patients experienced signs of congestive heart failure, and no hospitalizations were required for cardiotoxicity. Five (12%) patients had ten or more cycles and maintained normal ejection fractions.

There were six (14%) patients with Grade III hematological toxicity and eight (19%) patients experienced Grade IV hematological toxicity. In total, 14, 28 and 0% experienced Grade III hematological toxicity after 1, 2 and 2 or more years, respectively; 9, 16 and 22% experienced Grade IV hematological toxicity after 1, 2 and 2 or more years of treatment, respectively (**Table 3**). Three (7%) patients had febrile neutropenia. Seven (17%) patients required G-CSF support for neutropenia and all recovered.

Three (7%) patients experienced Grade III nonhematological toxicity (one case each of drug extravasation, perirectal abscess and staphylococcal infection). All patients completely recovered following treatment. No patients experienced Grade IV nonhematological toxicity (**Table 3**).

Keywords: mitoxantrone, secondary progressive multiple sclerosis

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Table 1. Patients and treatment history

Patient	Age	Sex	Disease duration (years)	EDSS before treatment	EDSS at last follow-up	Mitoxantrone dose (mg/m^2)	Number of cycles	Prior treatments	Treatments with mitoxantrone
1	49	F	5	8.0	8.0	12	3	Copaxone Avonex	None
2	52	F	25	8.0	8.0	12	9	Betaseron	Avonex
3	55	M	4	6.0	6.0	12	5	None	Avonex
4	57	F	3	3.5	3.5	12	9	None	Copaxone
5	51	M	10	7.5	7.5	12	7	T-cell vaccine Betaseron Avonex Copaxone Cytoxan	None
6	47	F	4	6.0	6.0	12	9	None	Avonex
7	30	F	10	7.5	7.5	12	4	None	Avonex
8	58	F	24	6.0	6.0	12	4	Betaseron	Avonex
9	50	F	18	7.5	7.0	12	5	None	Avonex
10	34	F	23	6.5	4.0	12	6	Copaxone	Betaseron
11	55	M	25	8.0	6.5	12	10	Copaxone Betaseron Cytoxan	None
12	46	M	7	6.5	6.5	12	2	Betaseron	Copaxone
13	46	F	12	7.5	7.5	12	2	Copaxone	Avonex
14	48	M	3	6.0	6.0	12	1	Copaxone	None
15	60	F	11	8.0	8.0	12	3	Betaseron Avonex	None
16	57	M	11	8.0	8.0	12	4	Betaseron	None
17	39	F	5	3.5	3.5	12	1	Copaxone	Betaseron
18	66	M	4	4.0	6.0	12	8	None	Avonex
19	49	F	1	6.0	6.5	12	5	None	Avonex
20	56	M	12	4.5	4.5	12	7	Copaxone Betaseron	Rebif
21	59	F	14	6.5	6.0	12	10	None	Betaseron
22	49	F	11	7.5	7.5	12	10	Betaseron Avonex	None
23	44	F	21	6.5	6.5	12	10	Avonex Betaseron DBS	None
24	54	F	15	7.0	7.0	12	3	Avonex Copaxone Rebif	None
25	65	M	16	7.5	7.5	12	1	T-cell vaccine	None
26	56	M	22	7.5	6.5	12	7	Copaxone	Betaseron
27	37	F	5	5.5	5.5	12	5	Avonex	Betaseron
28	45	M	6	8.0	7.0	12	4	Avonex	None
29	46	F	21	5.0	5.0	12	7	Betaseron	Copaxone
30	54	M	11	7.0	7.0	12	4	Copaxone Avonex	None
31	53	M	3	6.0	6.0	12	3	Betaseron	None

EDSS: Expanded Disability Status Scale; F: Female; M: Male.

Table 1. Patients and treatment history (cont.).

Patient	Age	Sex	Disease duration (years)	EDSS before treatment	EDSS at last follow-up	Mitoxantrone dose (mg/m^2)	Number of cycles	Prior treatments	Treatments with mitoxantrone
32	48	F	11	6.5	7.0	12	6	Betaseron Copaxone	None
33	49	F	5	6.0	6.0	12	1	Copaxone	Avonex
34	55	F	7	3.0	2.5	12	6	None	Copaxone
35	51	M	8	8.0	8.0	12	8	None	None
36	56	M	5	6.0	7.0	12	7	Avonex	Betaseron
37	54	M	15	8.0	8.0	12	12	Betaseron Cytoxan	None
38	56	M	20	6.0	6.5	12	5	None	Copaxone
39	54	M	10	3.5	6.5	12	9	Cytoxan	Betaseron
40	41	M	2	3.0	3.0	12	6	None	Avonex
41	34	M	16	6.0	6.0	12	4	None	Betaseron

EDSS: Expanded Disability Status Scale; F: Female; M: Male.

Discussion

In this study, 16% of patients had Grades I or II cardiotoxicity, but all patients available for repeat ECG off treatment had improvements in LVEF. Of patients re-evaluated off-study, none maintained an LVEF less than 50%. This suggests that, although cardiotoxicity is a concern, with regularly scheduled echocardiograms and asymptomatic cardiotoxicity (Grades I and II), it may not be permanent. Cardiotoxicity occurred at a median of 7.2 cycles (cumulative dose 84 mg/m^2), with the earliest being cycle four. These results suggest a schedule for monitoring cardiotoxicity that would include a baseline echocardiogram, followed by echocardiograms at 1 and 2 years, and every cycle of mitoxantrone thereafter. Additionally, in patients with depressed LVEF, post-treatment echocardiograms may be appropriate to confirm the findings of LVEF normalization, as observed in this study. Multiple gated acquisition scans may also represent a more accurate method of monitoring cardiotoxicity, in lieu of echocardiograms.

Hematological toxicity was frequent but reversible. In total, 17% of patients had recurrent Grade III or IV hematological toxicity, suggesting a cohort with susceptibility to myelosuppression. Grade III toxicity increased from 1 to 2 years of treatment, and Grade IV toxicity increased in all years of treatment, suggesting dose-dependent myelotoxicity. All patients requiring treatment with G-CSF responded with normalization of complete blood counts, including three patients with neutropenic fever. These results suggest that hematological toxicity, although common, is responsive to treatment. A CBC with differential should be checked on days 1 and 14 for each cycle of mitoxantrone. Should clinically significant myelosuppression occur, treatment with cytokines is indicated and will result in normalization of white blood cell counts.

Nonhematological toxicity was uncommon. One patient had a mitoxantrone injection-site reaction necessitating skin graft placement, but completely recovered; in order to reduce the risk of complications related to extravasation of

Table 2. Echocardiogram results confirming improvements in LVEF for each patient off treatment with mitoxantrone, with total cycles included per patient.

Total cycles	LVEF at baseline	LVEF nadir	LVEF off study
4	57%	47%	Normal
7	65%	50%	60%
8	60%	45%	60%
9	69%	55%	60%

LVEF: Left-ventricular ejection fraction.

Table 3. Hematological and nonhematological toxicity, Grades III and IV only.

Cycle	Hematological		Nonhematological	
	Grade III	*Grade IV*	*Grade III*	*Grade IV*
1–4 (n = 41)	6	4	2	0
5–8 (n = 25)	7	4	4	0
9–12 (n = 9)	0	2	0	0
Overall (n = 41)	6	8	6	0

Year 1 includes cycles 1–4, year 2 includes cycles 5–8 and year 2 or more includes cycles 9–12.

mitoxantrone, it should be given as a slow intravenous push over 30 min, with a nurse in attendance at all times. Two patients had Grade III infections and both responded to antibiotics. These results suggest serious nonhematological toxicity is uncommon and responsive to treatment.

Conclusion

In conclusion, although cardiac and hematological toxicity are common, both appear reversible with discontinuation of mitoxantrone or treatment with G-CSF and, if necessary, antibiotics. Nonhematological toxicity appears uncommon. When monitored appropriately, mitoxantrone is safe and effective in the treatment of SPMS.

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Highlights

- Mitoxantrone has established efficacy in patients with secondary progressive multiple sclerosis (SPMS), yet its usage is limited by toxicities, such as cardiotoxicity and myelosuppression.
- In this study, the toxicity of mitoxantrone treatment of SPMS was summarized.
- A total of 41 patients with SPMS were treated with mitoxantrone and their charts retrospectively reviewed for efficacy of treatment and frequency of toxicity.
- Although cardiac and hematological toxicity are common, both appear reversible with discontinuation of mitoxantrone or treatment with granulocyte colony-stimulating factor.

Bibliography

1. Goodin DS, Arnason BG, Coyle PK, Frohman EM, Paty DW: The use of mitoxantrone (Novantrone) for the treatment of multiple sclerosis: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 61, 1332–1338 (2003).
2. Avasarala JR, Cross AH, Clifford DB, Singer BA, Siegel BA, Abbey EE: Rapid onset Mitoxantrone-induced cardiotoxicity in secondary progressive multiple sclerosis. *Mult. Scler.* 9, 59–62 (2003).
3. Gonsette RE: Mitoxantrone immunotherapy in multiple sclerosis. *Mult. Scler.* 1, 329–332 (1996).
4. Ghalie RG, Edan G, Laurent M *et al.*: Cardiac adverse effects associated with mitoxantrone (Novantrone) therapy in patients with MS. *Neurology* 59, 909–913 (2002).
5. De Castro S, Cartoni D, Millefiorini E *et al.*: Noninvasive assessment of mitoxantrone cardiotoxicity in relapsing remitting multiple sclerosis. *J. Clin. Pharmacol.* 35, 627–632 (1995).
6. Gonsette RE: A comparison of the benefits of mitoxantrone and other recent therapeutic approaches in multiple sclerosis. *Expert Opin. Pharmacother.* 5(4), 747–765 (2004).
7. Gonsette RE: Mitoxantrone in progressive multiple sclerosis: when and how to treat? *J. Neurol. Sci.* 206, 203–208 (2003).
8. Ghalie RG, Mauch E, Edan G *et al.*: A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. *Mult. Scler.* 8(5), 441–445 (2002).
9. Edan G, Brochet B, Clanet M *et al.*: Safety profile of mitoxantrone in a cohort of 802 multiple sclerosis patients: a 4 year mean follow-up study. *Neurology* 62(Suppl. 5), A493 (2004).