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Final Results From the Registry to Evaluate Novantrone

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Abstract

Background: The Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis (RENEW) was a phase IV, multicenter, prospective, open-label, observational (OBS) study of mitoxantrone (MITO) in secondary-progressive multiple sclerosis (SPMS), progressive-relapsing multiple sclerosis (PRMS), and worsening relapsing-remitting multiple sclerosis (WRRMS).

Objective: To evaluate the tolerability and safety of MITO in the treatment of patients with worsening multiple sclerosis over a period of 5 years

Methods: The RENEW study included patients aged 18–65 years with WRRMS, SPMS, or PRMS who were undergoing treatment with MITO. MITO 12 mg/m^2 was infused intravenously every 3 months until a cumulative dose of 140 mg/m^2 was reached or therapy was discontinued. Patients were evaluated at baseline, every 3 months during therapy, and then annually for up to 5 years (OBS period). Complete blood cell and platelet counts and liver function tests were conducted before each dose of MITO. Left ventricular ejection fraction was measured at each scheduled evaluation and whenever clinically indicated. Serious adverse events (SAEs) were followed-up until the last visit.

Results: 509 patients were enrolled at 46 US centers and received at least 1 MITO infusion, of which 172 (33.8%) patients completed the 5-year OBS study period. Only 23 (4.5%) patients reached the maximum cumulative dose. The mean duration of treatment was 1.5 years, the mean (range) number of infusions was 6 (1–18), and the mean (range) cumulative dose was 69.8 (8.0–148.6) mg/m^2. 12 deaths were reported during the study. Relationship to study drug was assessed: probably related, n=1; possibly related, n=3; unrelated, n=7; unknown relationship, n=1. During the treatment phase, 143 SAEs were reported in 88 patients. During the OBS phase, 39 SAEs were reported in 23 patients. 10 patients experienced congestive heart failure (CHF) during the trial (treatment phase, n=6; OBS phase, n=4), and 3 patients developed leukemia. Over the entire trial, 60 cases of serious infections were reported in 41 (8.1%) patients. Amenorrhea developed in 28 (21.9%) women who reported regular menses at baseline.

Conclusion: Results of the RENEW study, including the rate of CHF and secondary leukemia, corroborate previously reported adverse events associated with MITO therapy, underscoring the need for appropriate risk-benefit assessment and close clinical, cardiac and hematologic monitoring before, during, and after MITO treatment.

Introduction

- Multiple sclerosis (MS) is a chronic and progressive disease that results in varying degrees of neurologic disability.
- Novantrone® (mitoxantrone for injection concentrate) is an immunosuppressive agent that was approved in 2000 to treat patients with worsening relapsing-remitting MS (WRRMS), secondary-progressive MS (SPMS), and progressive-relapsing MS (PRMS). It remains the only medication approved for these MS subtypes.[1]
- The Registry to Evaluate Novantrone Effects in Worsening Multiple Sclerosis (RENEW) was a 5-year, phase IV, multicenter, open-label, observational study designed to evaluate the safety of mitoxantrone therapy in patients with WRRMS, SPMS, and PRMS.

Purpose

- To present the final cumulative validated data from the beginning of the RENEW study in October 2000 through its completion in July 2008

Methods

- A total of 509 patients with MS receiving branded mitoxantrone were enrolled at 46 centers across the United States.
- Pending study inclusion, mitoxantrone was administered once every 3 months by intravenous infusion at 12 mg/m^2 until a cumulative dose of 140 mg/m^2 was reached, the patient or his or her physician chose to discontinue therapy, or an adverse event precluded further therapy.

Inclusion Criteria

- Clinically defined or laboratory-supported diagnosis of WRRMS, SPMS, or PRMS
- Age 18–65 years
- Platelet count >100,000 cells/μL
- Granulocyte count >2000 cells/μL
- Use of contraception throughout the trial and for 6 months following the last administration of mitoxantrone for women of reproductive age
- Signed informed consent

Exclusion Criteria

- Cardiac risk factors
  - History of congestive heart failure (CHF)
  - Left ventricular ejection fraction (LVEF) <50%
  - Previous treatment with mitoxantrone, other anthracenediones, or anthracyclines
  - Previous mediastinal radiotherapy or total lymphatic irradiation
- Aspartate transaminase, alanine transaminase, or bilirubin levels >2-fold higher than the upper limit of normal
- Pregnant or nursing
- Current urinary tract or other severe untreated infections

Assessments

- Patients were medically evaluated before treatment initiation, including the assessment of their score on the Kurtzke Expanded Disability Status Scale, and subsequently monitored regularly for 5 years from the date of treatment initiation (**Table 1**).
- Relapses were captured and treated per the investigator's discretion.
- At baseline, women were classified as having regular, irregular, or absent menses.
  - Women with regular or irregular menses were monitored for the development of on-study persistent amenorrhea (menses absent on ≥2 consecutive treatment visits and do not resume) or transient amenorrhea (resumption of menses after absence on ≥2 consecutive treatment visits).
  - Women with absent menses at baseline were monitored for resumption of menses (≥1 report of menses on-study).

Table 1. Patient Assessments

Assessment	Baseline	Treatment Phase: Before Every Infusion (Every 3 mo)	3 mo After Last Dose	Observational Phase: Annually After Dosing Completed
Medical history	X	X	X	X
Physical exam	X	X	X	X
Serum pregnancy test (if applicable)	X	X		
CBC and platelets	X	X	X	X
Liver function tests	X	X	X	
Signs and symptoms of CHF	X	X	X	X
LVEF monitoring with echo/MUGA	X	X	X	X

CBC=complete blood count; CHF=congestive heart failure; echo=echocardiogram; LVEF=left ventricular ejection fraction; MUGA=multiple gated acquisition scan.

Results

Patient Disposition and Demographics

- Of the 509 patients who enrolled in the RENEW study and received at least 1 dose of mitoxantrone, 172 (33.8%) completed the 5-year trial and 23 (4.5%) completed mitoxantrone treatment (reached a cumulative dose ≥132 mg/m^2).
- Reasons for discontinuation of therapy among 486 patients are shown in **Table 2**.

Table 2. Reasons for Discontinuation of Therapy

Reason for Discontinuation	Patients, n (%)
Death	4 (0.8)*
Adverse events	14 (2.9)
Physician decision	146 (30.0)
Lack of efficacy	16 (3.3)
Lost to follow-up	40 (8.2)
LVEF <50%	25 (5.1)
Clinically significant decrease in LVEF/CHF†	10 (2.1)
Patient request	132 (27.2)
Other	98 (20.2)
Unknown	1 (0.2)

CHF=congestive heart failure; LVEF=left ventricular ejection fraction.
*8 additional patients died after discontinuation.
†Clinical significance was determined by study site investigator.

- Patient characteristics at baseline are shown in **Table 3**.
- 97% of patients had received MS medications before study initiation. The most commonly received therapies at baseline were methylprednisolone intravenous (IV) (65%), oral prednisone (49%), interferon beta (IFNβ)–1a intramuscular (IM) (45%), IFNβ-1b subcutaneous (SC) (40%), and glatiramer acetate (GA; 40%).

Table 3. Patient Characteristics at Baseline

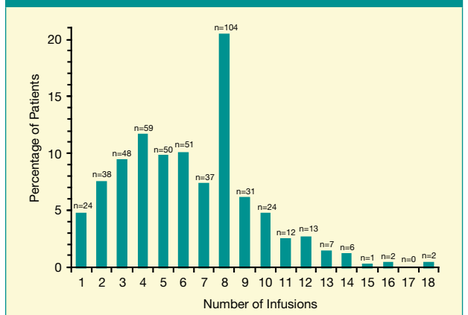
Characteristic	Overall	Worsening Relapsing-Remitting	Progressive Relapsing	Secondary Progressive
Patients enrolled,* n (%)	509 (100.0)	81 (15.9)	33 (6.5)	395 (77.6)
Mean age, y (range)	49 (19–68)	40 (19–63)	47 (30–64)	47 (25–68)
Women, %	67.6	77.8	54.5	66.6
White, %	88.6	85.2	87.9	89.4
History of MS				
Median EDSS score (range)	6.0 (0.0–9.0)	4.0 (1.0–8.0)	6.0 (1.5–8.5)	6.5 (0.0–9.0)
Median years since onset (range)	11.8 (0.4–45.3)	8.0 (0.4–29.2)	11.5 (0.6–34.5)	13.0 (0.6–45.3)
Median years since diagnosis (range)	8.6 (0.0–39.9)	4.8 (0.0–24.6)	7.3 (0.1–26.5)	9.3 (0.1–39.9)
Median years since most recent relapse (range)	0.4 (0.0–20.3)	0.2 (0.0–2.4)	0.2 (0.0–4.6)	0.5 (0.0–20.3)
Patients with no prior treatment for MS, n (%)	16 (3.1)	3 (3.7)	2 (6.1)	11 (2.8)
Women with regular menses, n (%)	128 (37.2)	34 (54.0)	7 (38.9)	87 (33.1)
Cardiac				
Mean LVEF, % (range)	62 (50–83)	62 (50–83)	63 (52–79)	62 (50–83)

EDSS=Kurtzke Expanded Disability Status Scale; LVEF=left ventricular ejection fraction; MS=multiple sclerosis.
*Patients with validated data who have received ≥1 dose of mitoxantrone.

Exposure to Therapy

- The mean duration of mitoxantrone treatment was 1.5 years (range, 0.0–4.9 y).
- Patients received a mean of 6 infusions (range, 1–18 infusions) during the study period (**Figure 1**).
- The mean cumulative dose per patient was 69.8 mg/m^2 (range, 8.0–148.6 mg/m^2). Doses <10 mg/m^2 were received by 121 (24%) patients and accounted for 517 (16%) of all infusions given during the study period.
- Of 509 patients enrolled in RENEW, 361 (71%) received concomitant therapy. The most commonly used concomitant therapies were GA (25%), methylprednisolone IV (21%), IFNβ-1a IM (21%), IFNβ-1b SC (15%), IFNβ-1a SC (12%), and oral prednisone (6%).

Figure 1. Number of Mitoxantrone Infusions per Patient



Relapses

- During the treatment phase of the trial, 185 relapses were reported in 120 patients.
- The median time to first relapse was 160 days (range 3–1215 d). Hospitalization was required for 36 (19%) relapses in 31 patients.
- During the observational phase of the trial, 60 relapses were reported in 40 patients. The majority (83%) did not require hospitalization.

Serious Adverse Events

- During the treatment phase of the study, a total of 143 serious adverse events (SAEs) were reported in 88 patients. Of these, 80 were considered unrelated to mitoxantrone therapy by investigators, 31 were considered probably or definitely related, 25 were considered possibly related, and 7 were categorized as having an unknown relationship to treatment (**Table 4**).

Table 4. Serious Adverse Events During the Treatment Phase Considered Definitely, Probably, or Possibly Related to Mitoxantrone Treatment

Serious Adverse Event	Number of Instances
Decreased ejection fraction	11 (10 probable, 1 possible)
Urinary tract infection	4 (3 probable, 1 possible)
Cardiomyopathy	3 probable
Febrile neutropenia	3 (1 definite, 1 probable, 1 possible)
Leukopenia	3 probable
Pneumonia	3 probable
Congestive heart failure	2 probable
Cellulitis gangrenous	1 probable
Herpes zoster	1 probable
Upper respiratory tract infection	1 probable
Urosepsis	1 probable
Ventricular hypokinesia	1 probable
Myocardial infarction	2 possible
Nausea	2 possible
Sepsis	2 possible
Septic shock	2 possible
Vomiting	2 possible
Abortion incomplete	1 possible
Cellulitis	1 possible
Deep vein thrombosis	1 possible
Dizziness	1 possible
Fungal skin infection	1 possible
Hydronephrosis	1 possible
Localized infection	1 possible
Lung infection	1 possible
Meningitis	1 possible
Pituitary tumor	1 possible
Pulmonary embolism	1 possible
Varicella	1 possible

- During the observational phase of the study, 23 patients experienced 39 SAEs, the most common being urinary tract infection (4 events in 3 patients) and road traffic accident (3 events in 3 patients).
- A total of 60 cases of serious infection were reported throughout the trial by 41 patients.
- 12 deaths were reported during the study (**Table 5**). Of these, 8 occurred during the treatment phase and 4 during the observational phase of the study.

Table 5. Deaths During the RENEW Study

Count	Cause(s)	Relationship to Mitoxantrone	Study Phase
1	Pneumonia	Unrelated	Treatment
2	Decreased ejection fraction, cardiomyopathy, CHF	Probable	Treatment
3	Pulmonary embolism	Unrelated	Treatment
4	Road traffic accident	Unrelated	Observational
5	Prostate cancer	Unrelated	Treatment
6	Cerebrovascular accident, carotid artery occlusion	Possible	Observational
7	Pulmonary edema	Unknown	Observational
8	Pulmonary embolism	Unrelated	Observational
9	Meningitis	Possible	Treatment
10	Respiratory failure	Unrelated	Treatment
11	Cardiopulmonary arrest	Unrelated	Treatment
12	Septic shock	Possible	Treatment

CHF=congestive heart failure.

Cardiac Function

- During the treatment phase, 413 postbaseline LVEF tests were performed for 202 patients, with an LVEF result of <50% reported in 27 patients. During the observational phase, 228 LVEF tests were performed for 136 patients, with an LVEF <50% reported in 14 patients (**Table 6**).
- 10 patients experienced CHF during the study, 6 during the treatment phase and 4 during the observational phase.

Table 6. Cardiac Adverse Events and Postbaseline Test of LVEF in Patients With ≥1 Infusion and ≥1 Additional Visit

	Treatment Phase (n=509)	Observational Phase (n=250)
Number of patients with CHF		
Requiring hospitalization	3	1
Without hospitalization	4*	3
Number of patients with postbaseline evaluations, n (%)		
LVEF <50%	27 (5.3)	14 (5.6)
LVEF <50% and ≥10% decrease relative to baseline LVEF†	25 (4.9)	14 (5.6)
LVEF ≥50% and ≥10% decrease relative to baseline LVEF	51 (10.0)	29 (11.6)
LVEF ≥10% increase relative to baseline LVEF	43 (8.4)	35 (14.0)

CHF=congestive heart failure; LVEF=left ventricular ejection fraction.
*6 patients total experienced CHF during the treatment phase; values above equal 7 because 1 patient was included in both categories.
†Test results with LVEF <50% and ≥10% decrease from baseline LVEF are a subset of those with LVEF <50%.

Leukemia

- Leukemia was reported in 3 patients.
- Of these, 2 were considered therapy related (1 case of acute myelogenous leukemia and 1 case of chronic myeloid leukemia); both occurred during the observational phase of the study.
- One case of acute promyelocytic leukemia was reported but is considered unrelated to mitoxantrone therapy.

Amenorrhea

- Of 128 women who reported regular menses at baseline, 28 (22%) developed persistent amenorrhea during the treatment phase of the study, and 5 (4%) developed transient amenorrhea.
- During the observational phase of the study, 4 (5%) women of 73 who reported regular menses at baseline developed persistent amenorrhea, and 1 (1%) developed transient amenorrhea.
- During the treatment phase of the study, resumption of menses was reported by 3 women who had reported an absence of menses at baseline; no such cases were reported during the observational phase.

Conclusions

- **The results of the RENEW study support the established benefit-risk profile of mitoxantrone.**
- **Risks associated with cardiotoxicity and increased incidence of secondary leukemia during mitoxantrone therapy underscore the importance of regular clinical, cardiac, and hematologic monitoring before every dose and follow-up after treatment.**
- **The long-term safety profile of mitoxantrone supports its continued use in the therapy of worsening forms of MS.**

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Reference

1. Novantrone® (mitoxantrone for injection concentrate). Full Prescribing Information, EMD Serono, Inc., Rockland, MA, 2009.