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Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required

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Abstract

The objective in this paper is to compare the cumulative incidence and incidence density of therapy-related acute myeloid leukaemia in two cohorts of patients with multiple sclerosis treated with mitoxantrone, and with previously reported data in the literature. Six new cases of acute myeloid leukaemia were observed by prospectively following two Spanish series of 142 and 88 patients with worsening relapsing multiple sclerosis and secondary-progressive disease treated with mitoxantrone. A literature review shows 32 further cases of acute myeloid leukaemia reported, 65.6% of which are therapy-related acute promyelocytic leukaemia. Five cases in the cohorts fulfilled the diagnostic criteria for acute promyelocytic leukaemia, and one patient was diagnosed with pre-B-acute lymphoblastic leukaemia. Acute myeloid leukaemia latency after mitoxantrone discontinuation was 1 to 45 months. The accumulated incidence and incidence density was 2.82% and 0.62%, respectively, in the Valencian cohort, and 2.27% and 0.44% in the Catalonian cohort. In the only seven previously reported series, the accumulated incidence varied from 0.15% to 0.80%. The real incidence of acute myeloid leukaemia after mitoxantrone therapy in the multiple sclerosis population could be higher as evidenced by the growing number of cases reported. Haematological monitoring should continue for at least 5 years after the last dose of mitoxantrone. These data stress the necessity of re-evaluating this risk.

Keywords

chemotherapy, haematological study, incidence study, mitoxantrone, multiple sclerosis, secondary leukaemia

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Introduction

The development of therapy-related acute myeloid leukaemia (t-AML) has been significantly correlated to previous treatment with several cytostatic drugs. Mitoxantrone (MTZ) is an anthracenedione with potent anti-inflammatory and immunomodulating propierties,[1,2] approved by the US Food and Drug Administration and the European Union for patients with multiple sclerosis (MS) with worsening relapsing–remitting MS (RRMS) (or progressive relapsing MS) and secondary-progressive MS (SPMS). The efficacy of MTZ in MS has been previously reported in randomized therapeutic trials[3,4] and follow-up studies.[5–7] However, MTZ can also induce the cleavage of DNA mediating the formation of chromosomal translocation breakpoints, leading to secondary leukaemia. Although MTZ appears to have a low potential to cause secondary leukaemia at the recommended dose,[8,9] the real incidence of t-AML after MTZ therapy in the MS population is difficult to calculate as the number of patients with MS exposed to MTZ in post-marketing

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is unknown and spontaneous reporting of adverse events can be subject to under-reporting. The onset of t-AML may occur up to 5 years after treatment withdrawal, whereas follow-up studies are usually shorter.

The aim of this study was to describe the incidence of t-AML in two cohorts of patients with MS treated with MTZ, and to review and compare with the incidences reported in the literature.

Materials and methods

From two cohorts of Mediterranean MS patients, we enrolled consecutive patients with aggressive RRMS and SPMS treated with MTZ: the Valencian Community (VC) cohort, which includes the seven hospitals where MTZ has been administered, and the Vall d'Hebron (VH) cohort from Catalonia. These centres usually work in common investigational projects and represent similar population groups. All patients received their first course of MTZ between February 2001 and January 2007. The observation period extended to December 2007. The follow-up protocol included scheduled visits on the day of MTZ infusion and every 3 months after the last dose; haematological study on the day of MTZ infusion and every 3 months after the last dose; and isotopic ventriculography at baseline and after every 30 mg/m^2 of MTZ received as well as one year and five years after the last dose. The maximum dose allowed was 120 mg/m^2.

MTZ was offered to patients with RRMS or SPMS with (inclusion criteria): (1) poor response to other immunomodulating therapy defined by two or more relapses and/or persistent disability defined by an Expanded Disability Status Scale (EDSS)[10] increase of at least 1.0 point in the previous year, out of relapses; (2) baseline EDSS >3.0 or ≤ 6.5; (3) normal baseline blood test and echocardiography (ejection fraction $>50\%$ and no structural anomalies); and (4) signed informed consent. Patients were treated with one of the following four regimens: regimen A, 10–12 mg/m^2 per month for 3 months followed by 10–12 mg/m^2 every 3 months for patients with one or more relapses in the previous year and sustained EDSS increase of at least 1.0 point; regimen B, 10–12 mg/m^2 every 3 months for patients with an increase of at least 1.0 point in the EDSS in 1 year out of relapses; regimen C, 10 mg/m^2 per month for 3 months followed by immunomodulatory therapy for patients treated with immunomodulators with two or more relapses in one year and no progression in disability; and regimen D, 5 mg/m^2 every 3 months for patients with sustained disability progression and with clinical characteristics that made a lower dose advisable for better tolerance.

Per protocol, treatment was discontinued in the following cases: (1) $>10\%$ decrease in left ventricular ejection fraction (LVEF) with respect to baseline or LVEF $<50\%$ at any time; (2) repeated infection; (3) granulocytopenic fever; (4) leukopenia <1000 cells per mm^3 or suspected leukaemia; or (5) elevated liver enzymes or other abnormal laboratory results such as high creatinine or bilirubin count. This protocol was approved by the ethic committees of all participating centres.

Analysis included comparison of the cohort characteristics, cumulative incidence of t-AML as the ratio between the number of cases treated and the total population, and incidence density, as the ratio between the number of cases and the sum of years from the start of the first treatment to the last clinical evaluation or case that occurred.

Results

Between 2001 and 2007, 230 patients with MS received MTZ: 142 patients in the VC cohort and 88 patients in the VH cohort. Demographic and clinical characteristics are shown in Table 1. There were significant differences between the two series, except for the MTZ dose administered. Patients were younger in the VH cohort, both at the beginning of the disease and at the start of

Table 1. Demographical and clinical characteristics of the series

	Total series $n=230$ mean (range)	**Valencian Community series** $n=142$ mean (range)	**Vall d'Hebrón Hospital series** $n=88$ mean (range)	p-value (**<0.001**)
Age at the onset of the disease (years)	28.2 (10–62)	30.0 (11–62)	25.3 (10–53)	0.000
Age at the beginning of MTZ (years)	39.2 (19–68)	42.0 (22–68)	34.4 (19–56)	NS
Evolution time at treatment (years)	10.9 (0–37)	12.0 (0–37)	9.1 (1–28.8)	0.000
Time in treatment (months)	15.4 (1–50)	18.0 (1–50)	11.1 (1–23)	0.000
Follow-up since the end of treatment (years)	3.4 (1–7.9)	3.0 (1–7.4)	4.2 (1–7.9)	0.000
Doses of MTZ administrated (mg/m^2)	*66.9 (10–120)*	*66.9 (10–120)*	*66.5 (12–72)*	*NS*

MTZ treatment, and the evolution time at treatment initiation was shorter. During follow-up, four patients from the VC cohort were diagnosed with acute promyelocytic leukaemia (t-APL) and two patients from the VH cohort were diagnosed with leukaemia, one with t-APL and one with acute lymphoblastic leukaemia (ALL).

The cumulative incidence of t-AML in the VC cohort was 2.82% (95% CI, 1.2–4.4), and the incidence density was 0.62% person per year (95% CI 0.0–1.2). The VH cohort showed a cumulative incidence of t-AML of 2.27% (95% CI 1.1–3.4), and an incidence density of 0.44% person per year (95% CI 0.0–1.2). The global incidence density was 0.55% person per year (95% CI 0.1–0.9) We found no relation between the occurrence of t-AML and dose administered, age at the beginning of the disease or at beginning of the treatment, disease duration, sex or concomitant medications.

The literature review revealed 32 cases of t-AML reported, 21 of which were t-APL. t-AML latency ranged from 1 to 60 months after treatment discontinuation. Only nine series of t-AML have been reported (see Table 2) [11–32], and in the largest series (1378 patients from three MS studies), four cases of t-AML were described with an observed incidence of 0.29% (95% CI, 0.00–0.40%).[12] In the other eight series, which included 59,[17] 255,[19] 644,[20] 25,[23] 250,[25] 400,[26] 170,[28] and 61[31] patients, the calculated incidence varied from 0.15% to 0.80%. The most common reported leukaemia related with MTZ therapy is t-APL (12 cases out of the 21 cases reported, 57.1%); other types of leukaemia reported are: four cases of M4 (19.0%); one case of M1 (4.7%); one case of M5 (4.7%); one case of ALL (4.7%) and one case of chronic myeloid leukaemia (4.7%); one case was reported as non-lymphoblastic acute leukaemia, without specification of the type of leukaemia (see Table 2).

Finally, we studied the year of diagnosis of the leukaemia in all cases, to determine whether there was a tendency towards increment in the incidence. The only unknown year of diagnosis is the case reported by Goodkin[14] and Tanasesku et al.,[15] in which the year previous to the first report was considered as the year of diagnosis. This analysis showed that, considering the cases reported, the incidence of t-AML has not varied significantly along the years since 2001 (2–5 cases per year).

Case studies

Case 1 (Valencian Community cohort)

In May 2004, a 52-year-old woman was diagnosed with SPMS with superimposed relapses. Her disability had increased in the last year (from 6.0 to 6.5), and continued to deteriorate despite steroid therapy and plasma exchange. From December 2004 to March 2005 she received 10 mg/m^2 MTZ every month for 3 months, and continued therapy with azathioprine. Disability stabilized at EDSS 6.5. In December 2005 the patient suffered another exacerbation and discontinued azathioprine, starting treatment with interferon beta-1b.

In February 2007, 23 months after MTZ therapy was discontinued, the patient developed fever and fatigue, with severe pancytopenia in the blood analysis. APL was then diagnosed; a cytogenetic analysis showed t(15; 17) (q22; q21), bcr1 PML breakpoint with *PML-RARalpha* rearrangement. The patient was treated according to the PETHEMA protocol[31] with an induction cycle with idarubicin and all-*trans*-retinoic acid (ATRA), and a consolidation cycle with idarubicin, cytarabine, and ATRA. After complete remission in May 2007 which lasted only a short time, the patient received a second cycle of consolidation with idarubicin and cytarabine. Finally, 6 months after chemotherapy she developed a brain haemorrhage secondary to severe thrombocytopenia and died.

Case 2 (Valencian Community cohort)

A 23-year-old man with MS diagnosed in 1999 had received interferon beta-1a from July 2000 to September 2004, when therapy was discontinued as he had two relapses and cumulative disability (EDSS 5.0). He was then treated with MTZ, 10 mg/m^2 once a month for 3 months (October 2004 to January 2005) followed by 10 mg/m^2 every 3 months for 24 months. The total MTZ dose administered was 100 mg/m^2; during this time the patient did not experience new exacerbations or progression of disability.

In March 2007, 2 months after the final MTZ dose, the patient went to the MS Unit for an unscheduled visit related to fever, sore throat, and bruises on the body and limbs in the previous 48 hours. Blood tests showed severe pancytopenia. The patient was diagnosed with APL, t(15; 17), bcr1 positive, and treated under the PETHEMA protocol. At present, he is in complete remission and continues consolidation treatment.

Case 3 (Valencian Community cohort)

Case 3 is a 59-year-old woman with RRMS since 1987, with relapses and progression of disability (EDSS in January 2004, 4.5), which motivated therapy with MTZ, 10 mg/m^2 every 3 months until May 2005. During treatment the patient remained stable. Total MTZ dose received was 70 mg/m^2. In April 2006, the

Table 2. Therapy-related leukaemia in multiple sclerosis patients treated with MTZ: literature review

Author	*N*	Sex, Age	Total Dose (mg)	t-AML Type	Combined Therapy*	t-AML Latency	Outcome (CR in months)
Vicari, 1998[11]	–	M, 36	87.5	APL (M3)	No	60	CR (12 m)
Ghalie, 2002[12] and Brassat, 2002[13]	1378	F, 30	120	AML (M5)	No	15	Death
Goodkin, 2003[14] and Le Page, 2008[7]		F, 32	70	AML (M4)	Uk	–	CR (70 m)
Goodkin, 2003[14] and Tanasescu, 2004[15]		M, 43	160	AML (M1)	Cy predose MTZ	1	CR (4 m)
Beaumont, 2003[16]	–	F, 28	120	APL (M3)	MTZ (predose MTZ)	16	CR (35 m)
Heesen, 2003[17]	59	F, 34	108	AML (M4eo)	Aza and MTX (predoseMTZ)	5	CR (14 m)
Cattaneo, 2003[18]	–	M, 56	198	APL (M3)	INF-b (predose MTZ)	14	CR (1 m)
Delisse, 2004[19]	255	F, 34	120	APL (M3)	No	26	Death
Voltz, 2004[20]	644	F, 45	84	AML (M4eo)	No	28	CR (24 m)
Novoselac, 2004[21]	–	–	–	APL (M3)	Uk	11	CR (Uk)
Mistry, 2005[22]	–	M, 42	110	APL (M3)	No	7	CR (Uk)
Arruda, 2005[23]	25	F, 47	15	APL (M3)	IFN-b (predose MTZ)	30	Death
Nollet, 2006[24]	–	F, 37	58.3	APL (M3)	Uk	18	CR (10 m)
	–	F, 50	160	AML (M4)	Aza (postdose MTZ)	27	Death
Ledda, 2006[25]	250	F, 21	170	APL (M3)	IFN-b (predose MTZ)	18	CR (4 m)
		F, 37	147.5	APL (M3)	No	5	CR (4 m)
Cartwright, 2007[26]	400	F, 40	120	ALL	INF-b (predose MTZ)	6	CR (11 m)
Sumrall, 2007[27]	–	M, 58	–	AML	–	–	–
Cordioli, 2007[28]	170	F, ?	60	APL (M3)	Uk	–	–
		F, ?	22.5	APL (M3)	Uk	–	–
		F, ?	130	APL (M3)	Uk	–	–
Sadiq, 2008[29]	–			CML			
Ramkumar, 2008[30]	–	M, 51	170	APL (M3)	IFN-b (predose MTZ)	22	CR (1.5 m)
Pielen, 2008[31]	61	F, 56	96	APL (M3)	Uk	22	–
		M, 54	84	AML (M2/4)	Uk	2	
	–	F, 48	96	APL (M3)	No	24	CR (10 m)
VC-Case 1[32]	230	F, 52	30	APL (M3)	Aza (predose MTZ) IFN-b (postdose MTZ)	23	Death
VC-Case 2		M, 23	100	APL (M3)	No	3	CR (8 m)
VC-Case 3		F, 59	70	APL (M3)	No	11	CR (6 m)
VC-Case 4		F, 33	60	APL (M3)	No	1	Death
VH-Case 5		F, 26	137	ALL	IFN-b (predose MTZ)	8	Death
VH-Case 6		M, 44	159	APL (M3)	IFN-b (predose MTZ)	45	CR (10 m)

APL, Acute promyelocytic leukaemia; AML, Acute myeloblastic leukaemia; ALL, Acute lymphoblastic leukaemia; CML, Chronic myeloid leukaemia; INF-b, Interferon beta; Aza, azathioprine; MTX, methotrexate; Cy, cyclophosphamide; predose, previously to MTZ therapy; postdose, after MTZ discontinuation; CR, complete remission; Uk, Unknown.
*Combined therapy, immunosuppressant or immunomodulator agents before or after MTZ therapy.

patient presented with spontaneous diffuse haematomas over the entire body surface. Laboratory tests showed severe pancytopenia and prolonged bleeding time. APL was diagnosed; cytogenetic analysis showed t(15; 17), bcr1 positive. The patient was treated with the PETHEMA protocol. Since September 2006, the patient has been in complete remission and is receiving maintenance therapy.

Case 4 (Valencian Community cohort)

A 33-year-old woman had developed RRMS 15 years earlier, but had refused treatment with interferon beta and was only receiving intravenous methylprednisolone for relapses. When she first presented at the outpatient clinic in 1996, the EDSS score was stable at 4.5. By 2001, her EDSS score worsened to 6.0 and treatment

with azathioprine (50 mg per day) was started and immediately discontinued due to adverse effects. In November 2005, with an EDSS score of 7.0, MTZ therapy was initiated at 10 mg/m^2 every 3 months and applied six times up to June 2007. In July 2007 she experienced fever and diffuse haematomas and was admitted to the hospital with a diagnosis of APL, where she received induction therapy. The patient developed severe anorexia, depression and considerable loss of weight. In September 2007, 4 months after chemotherapy, she died from a bacterial lung infection.

Case 5 (VH)

A 26 year-old woman with RRMS since 1997, who had been treated with interferon beta 1-b from August 1998 until March 2002, when MTZ was started (12 mg/m^2 monthly for 3 months and then 3-monthly until complete one year). The patient received a total dose of 137 mg/m^2. The last administration was in March 2003, and continued therapy with glatiramer acetate. During this period she had no relapses and no disability progression. In November 2003, 8 months after last MTZ infusion, she complained of spontaneous skin hematomas. The haematological study was consistent with pre B-acute lymphoblastic leukaemia; the cytogenetic analysis showed a t(4, 11) (q21; q23). The patient received induction chemotherapy with vincristine, daunoblastine, intrathecal methotrexate, cytarabine, and hydrocortisone, followed by consolidation therapy with intravenous vincristine, methotrexate, cytarabine, asparaginase, 6-mercaptopurine and hydrocortisone. In 2004 she experienced adequate response, but soon developed pulmonary aspergillosis and died from massive haemoptysis.

Case 6 (Vall d'Hebron cohort)

A 44-year-old man diagnosed with SPMS developed APL after receiving MTZ treatment. The patient was first seen at the Vall de Hebron unit in 1999 and started on interferon beta-1a treatment in October 1999 (EDSS 3.5). Despite the immunomodulatory drug, his disability progress continued to worsen. By late 2001 he had EDSS 6.0. In February 2002 interferon was replaced with MTZ, with the same protocol as in the previous case. He received a total dose of 159 mg/m^2, with the last infusion on January 2003. In February 2007 he was admitted to the hospital for gingival bleeding, spontaneous skin bruises and fever. The study revealed APL and the cytogenetics showed t(15; 17). Induction chemotherapy with ATRA and idarubicin achieved excellent response, followed by a consolidation period with oral ATRA. At the time of writing, the patient was in remission.

Discussion

The aim of this study was to compare the incidence of t-AML in patients with MS after MTZ treatment in our series (VC series), with a similar series from the same geographic area (VH series). The main data of our study are similar cumulative incidences of t-AML for the two series, with values higher than the previously reported. Patients treated in the VH cohort were significantly younger, both for disease beginning and for age at MTZ start, and had shorter disease duration, although MTZ dose was similar in both cohorts. Nevertheless, we found no relation between the occurrence of t-AML and dose administered, age at the beginning of the disease or at beginning of the treatment, disease duration, treatment scheme, sex or concomitant medications. There was no t-AML in the group of MS patients treated with the low-dose scheme (regimen D), which was chosen for patients whose clinical characteristics led us to select a lower dose to ensure better tolerance, but the low number of patients treated in this group does not enable us to draw significant conclusions.

According to the type of chemotherapy used, two forms of t-AML have been described: t-AML after treatment with alkalizing substances, related to complex cytogenetic changes (chromosome deletions or losses, primarily chromosomes 5 and 7), and proceeded by a longer preleukaemic phase (myelodysplastic syndrome),[33–35] and t-AML following DNA topoisomerase II inhibitors, such as anthracyclines, or MTZ.

This second form usually has an acute onset, a short latency period (12–36 months), and is associated with cytogenetic abnormalities similar to those of de novo acute leukaemia (e.g. translocations involving 8; 21 or 15; 17 11q23 band or inv [16]). A specific subtype of t-AML is the t-APL (type M3 according to the French–American–British classification). t-APL is characterized by blast morphology, a translocation, t15; t17 or t8; 21 which leads to promyelocytic leukaemia-retinoic acid receptor alpha (*PML-RARalpha*) rearrangement[36] at the molecular level, and specific differentiation of blast cells by ATRA.[37] It usually responds to ATRA and several induction chemotherapies, although reported survival after eight years is 59%.[37] About 200 cases of t-APL have been reported in the literature to date, although it has been increasing in recent years among patients previously treated with topoisomerase II inhibitors, particularly in those with prior malignant disease.[22] All leukaemia cases in our series except for one were APL. These five cases met the diagnostic criteria for t-APL; all had received chemotherapy

before the onset of leukaemia, none had personal or family history of malignancy, and none had any known leukogenic risk factors.[17] Only one patient had been temporarily treated with another immunosuppressant agent (azathioprine) after MTZ discontinuation, and although MTZ is the probable cause for the chromosomal translocation, sequential immunosuppressive therapies could have contributed to clonal expansion of malignant haematopoietic progenitors. In our series, no relation was found with the previous or subsequent treatment with immunosuppressants or immunomodulators. Cytogenetically, all five patients had t(15; 17) translocation, and morphologically all cases had typical hypergranular APL (M3). The time between MTZ discontinuation and t-APL diagnosis ranged from 1 to 45 months (median, 22.5 months). Including literature review data, t-AML latency ranged from 1 to 60 months.

Finally, three patients achieved complete remission 3 to 6 months after therapy, with good response to ATRA and several chemotherapy induction protocols. The other two patients died, one from an opportunistic infection and other from a haematological complication. The remaining patient was diagnosed with pre B-acute lymphoblastic leukaemia, which has a worse prognosis; despite the initial good response, she died from an opportunistic infection. Four of these cases were previously reported in a letter to raise concerns.[32]

In patients with malignant diseases, the incidence of t-AML observed after MTZ therapy combined with other chemotherapy agents has been reported as 2% to 12%.[25] In patients with MS, in whom MTZ is usually used as the only immunosuppressant agent, few series have been reported, and the calculated incidence varied from 0.15% to 0.80%. A common limitation for determination of the real incidence of t-AML in the different studies is the short time of follow-up after MTZ discontinuation. In the case of MS patients treated with MTZ there are also important methodological limitations.

The fact is that there are only a few reported series of patients with MS followed prospectively after MTZ therapy: 124 patients in the MIMS trial,[38] of which some received only 5 mg/m^2 every 3 months; 100 patients in the French–British study;[3,7] studies with 27 patients[4] and 28 patients;[39] and one of the largest studies,[12,13] which included 1378 patients and was based on general data of t-AML incidence, is retrospective. This series was collected retrospectively, included patients who had begun MTZ treatment from 1992 to 2001 and was reported in 2002. Moreover, and related to this study, only one case of t-AML was reported in the first analysis and two new cases were communicated from the same cohort one year later.[26] The same occurred with the series of 100 MS patients treated with MTZ and reported by Le Page et al.[7] in 2008; regarding the same series, the authors did not report cases of t-AML in 2006,[40] and one new case was communicated two years later. On the other hand, the other largest observational study (RENEW),[8] which is useful in defining the expected values of cumulative incidence of t-AML in the MS population, has been recently closed and the results presented at the World Congress on MS.[41] Three new cases of t-ALM have been described during the follow-up, two possibly related to MTZ therapy, although it is necessary to say that with the data presented is not possible to define the total number of patients treated and duration of treatment. Of 470 patients who stopped treatment, 296 (62.2%) had not been followed for 5 years and 121 (23.7%) had received MTZ at doses lower than 10 mg/m^2. Therefore, if we consider these three new cases related to the group of MS patients followed for almost five years, or to the group of MS patients treated with doses of 10 mg/m^2, t-AML incidence is in any case higher than the value proposed by the French–British study. According to the intervals of the global incidence density we can expect up to one case of secondary leukaemia in the next months.

Finally, we think that all these data merit serious consideration and stress the necessity to review the real risk of t-AML in relation to MTZ therapy. The authors propose that a systematic review and a search strategy might be considered by the international community.

Longer observation time after MTZ therapy seems to be the most important factor for t-AML incidence data although other possible factors could be considered in observational studies, such as sequential treatment with another immunosuppressant agents, different protocols of treatment and follow-up, and a possible genetic predisposition in the MS population. However, the fact is that our data are consistent across two similar series, that different schemes of treatment failed to minimize side effects, and that the assessment of the impact of t-AML after MTZ discontinuation, usually considered as small, should be revised as it is based on data from short series that are not always prospective.

The most common leukaemia related to MTZ therapy for MS is t-APL (17 cases out of the 27 cases reported, 62.9%), although there are other types of leukaemia associated with MTZ. We report in this paper the second case of ALL,[26] and recently the first case of MTZ-related chronic myeloid leukaemia has also been reported.[29] This high incidence of t-APL in the MS population could be related to a specific association. Thus, the analysis of 12 cases of MTZ-related t-APL in patients with MS revealed an altered distribution of chromosome 15 breakpoints compared

to de novo APL, biased towards disruption within *PML* intron 6 (11/12, 92% versus 622/1022, 61%: $p = 0.035$).[42] This recently reported study supports the presence of preferential sites of DNA damage induced by MTZ in *PML* and *RARA* genes that may underlie the propensity to develop this subtype of leukaemia after exposure to this agent. Therefore, it would be important to assess prospectively the true occurrence of t-APL developed in the MS population, with and without MTZ treatment, and to instigate further studies to investigate whether patients with MS could have a particular predisposition to the development of t-APL.

Conclusions

The true incidence of t-AML after MTZ for MS is not known and might be higher than previously suspected. These data should alert MS clinicians about a potentially elevated risk of t-AML in MS patients after MTZ treatment. We propose a cautious selection of candidates and a longer follow-up to improve patient safety during and after MTZ therapy.

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References

1. Fidler JM, DeJoy SQ, Gibbons Jr JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. I. Suppression of b lymphocyte function. *J Immunol* 1986; 137: 727–732.
2. Fidler JM, DeJoy SQ, Smith III FR, Gibbons Jr JJ. Selective immunomodulation by the antineoplastic agent mitoxantrone. II. Nonspecific adherent suppressor cells derived from mitoxantrone-treated mice. *J Immunol* 1986; 136: 2747–2754.
3. Edan G, Miller D, Clanet M, et al. Therapeutic effect of mitoxantrone combined with methylprednisolone in multiple sclerosis: a randomised multicenter study of active disease using mri and clinical criteria. *J Neurol Neurosurg Psychiatry* 1997; 62: 112–118.
4. Millefiorini E, Gasperini C, Pozzilli C, et al. Randomized placebo-controlled trial of mitoxantrone in relapsing–remitting multiple sclerosis: 24-month clinical and MRI outcome. *J Neurol* 1997; 244: 153–159.
5. Debouverie M, Taillaqndier L, Pittion-Vouyovitch S, Vespignani H. Clinical follow-up of 304 patients with multiple sclerosis three years after mitoxantrone treatment. *Mult Scler* 2007; 13: 626–631.
6. Buttinelli C, Clemenzi A, Borriello G, Denaro F, Pozzilli C, Fieschi C. Mitoxantrone treatment in multiple sclerosis: a 5-year clinical and MRI follow-up. *Eur J Neurol* 2007; 14: 1281–1287.
7. Le Page E, Leray E, Taurin G, et al. Mitoxantrone as induction treatment in aggressive relapsing remitting multiple sclerosis: treatment response factors in a 5 year follow-up observational study of 100 consecutive patients. *J Neurol Neurosurg Psychiatry* 2008; 79: 52–56.
8. Smith CH, Lopez-Bresnahan MV, Beagan J. Safety and tolerability of novantrone® (mitoxantrone) in clinical practice: status report from the registry to evaluate novantrone® effects in worsening MS (RENEW) study. *Neurology* 2004; 62(Suppl 5): A489.
9. Edan G, Brochet B, Clanet M. Safety profile of mitoxantrone in a cohort of 802 multiple sclerosis patients: a 4 year mean follow-up study. *Neurology* 2004; 62(Suppl 5): A493.
10. Kurtzke JF. Rating neurological impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology* 1983; 33: 144–152.
11. Vicari AM, Ciceri F, Folli F, et al. Acute promyelocytic leukemia following mitoxantrone as single agent for the treatment of multiple sclerosis. *Leukemia* 1998; 12: 441–442.
12. Ghalie RG, Mauch E, Edan G, et al. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. *Mult Scler* 2002; 8: 441–445.
13. Brassat D, Recher MD, Waubant E, et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with ms. *Neurology* 2002; 59: 954–955.
14. Goodkin DE. Therapy-related leukemia in mitoxantrone-treated patients. *Mult Scler* 2003; 9: 426.
15. Tanasescu R, Debouverie M, Pittion S, Anxionnat R, Vespignani H. Acute myeloid leukaemia induced by mitoxantrone in a multiple sclerosis patient. *J Neurol* 2004; 251: 762–763.
16. Beaumont M, Sanz M, Carli PM, et al. Therapy-related acute promyelocytic leukemia. *J Clin Oncol* 2003; 21: 2123–2137.
17. Heesen C, Bruegmann M, Gbdamosi J, Koch E, Mönch A, Buhmann C. Therapy-related acute myelogenous leukaemia (t-AML) in a patient with multiple sclerosis treated with mitoxantrone. *Mult Scler* 2003; 9: 213–214.
18. Cattaneo C, Almici C, Borlenghi E, Motta M, Rossi G. A case of acute promyelocytic leukaemia following mitoxantrone treatment of multiple sclerosis. *Leukemia* 2003; 17: 985–986.
19. Delisse B, de Seze J, Mackowiak A, et al. Therapy related acute myeloblastic leukaemia after mitoxantrone treatment in a patient with multiple sclerosis. *Mult Scler* 2004; 10: 92.
20. Voltz R, Starck M, Zingler V, Strupp M, Kolb HJ. Mitoxantrone therapy in multiple sclerosis and acute

leukaemia: a case report out of 644 treated patients. *Mult Scler* 2004; 10: 472–474.
21. Novoselac AV, Reddy S, Sanmugarajah J. Acute promyelocytic leukemia in a patient with multiple sclerosis following treatment with mitoxantrone. *Leukemia* 2004; 18: 1561–1562.
22. Mistry AR, Felix CA, Whitmarsh RJ, et al. DNA topoisomerase ii in therapy-related acute promyelocytic leukemia. *N Engl J Med* 2005; 352: 1529–1538.
23. Arruda WO, Montú MB, de Oliveira Mde S, Ramina R. Acute myeloid leukaemia induced by mitoxantrone: case report. *Arq Neuropsiquiatr* 2005; 63: 327–329.
24. Nollet S, Berger E, Deconinck E, Baldauf E, Rumbach L. Acute leukaemia in two multiple sclerosis patients treated with mitoxantrone. *Rev Neurol (Paris)* 2006; 162: 195–199.
25. Ledda A, Caocci G, Spinicci G, Cocco E, Mamusa E, La Nasa G. Two new cases of acute promyelocytic leukemia following mitoxantrone treatment in patients with multiple sclerosis. *Leukemia* 2006; 20: 2217–2218.
26. Cartwright MS, Jeffery DR, Lewis ZT, Koty PP, Stewart WT, Molnar I. Mitoxantrone for multiple sclerosis causing acute lymphoblastic leukemia. *Neurology* 2007; 68: 1630–1631.
27. Sumrall A, Dreiling B. Therapy-related acute nonlymphoblastic leukemia following mitoxantrone therapy in a patient with multiple sclerosis. *J Miss State Med Assoc* 2007; 48: 206–207.
28. Cordioli C, Cattaneo C, Rossi G, Capra R. Analysis of incidence, risk factors and prognosis of acute promyelocytic leukaemia related to mitoxantrone therapy in multiple sclerosis patients. *Neurology* 2007; 68(Suppl 1): A276.
29. Sadiq SA, Rammal M, Sara G. Chronic myeloid leukemia associated with mitoxantrone treatment in a patient with ms. *Mult Scler* 2008; 14: 272–273.
30. Ramkumar B, Chadha MK, Barcos M, Sait SN, Heyman MR, Baer MR. Acute promyelocytic leucemia alter mitoxantrone therapy for multiple sclerosis. *Cancer Genet Cytogenet* 2008; 182: 126–129.
31. Pielen A, Goffette S, van Pesch V, Gille M, Sindic JM. Mitoxantrone-related acute leukemia in two ms patients. *Acta Neurol Belg* 2008; 108: 99–102.
32. Bosca I, Pascual AM, Casanova B, Coret F, Sanz MA. Four new cases of therapy-related acute promyelocytic leukaemia after mitoxantrone. *Neurology* 2008; 71: 457–458.
33. Sanz MA, Martín G, González M, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the pethema group. *Blood* 2004; 103: 1237–1243.
34. Then Bergh F, Niklas A, Strauss A, et al. Rapid progression of myelodysplastic syndrome to acute myeloid leukemia on sequential azathioprine. ifn-beta and copolymer-1 in a patient with multiple sclerosis. *Acta Haematol* 2006; 116: 207–210.
35. Su YW, Chang MC, Chiang MF, Hsieh RK. Treatment-related myelodysplastic syndrome after temozolomide for recurrent high-grade glioma. *J Neurooncol* 2005; 71: 315–318.
36. Grudeva-Popova J, Yaneva M, Zisov K, Ananoshtev N. Therapy-related acute promyelocytic leukemia after treatment with radioiodine for thyroid cancer: case report with literature review. *J BUON* 2007; 12: 129–132.
37. Balakrishnan C, Pathan E, Khodaiji S, Dasgupta A, Mangat G, Joshi VR. Myelodysplasia and acute myeloid leukaemia in a case of rheumatoid arthritis with secondary amyloidosis treated with chlorambucil. *J Assoc Physicians India* 2004; 52: 423–425.
38. Hartung HP, Gonsette R, König N, et al. Mitoxantrone in progressive multiple sclerosis: a placebo-controlled, double-blind, randomised, multicentre trial. *Lancet* 2002; 360: 2018–2025.
39. van de Wyngaert FA, Beguin C, D'Hooghe MB, et al. A double-blind clinical trial of mitoxantrone versus methylprednisolone in relapsing, secondary progressive multiple sclerosis. *Acta Neurol Belg* 2001; 101: 210–216.
40. Le Page E, Leray E, Taurin G, Coustans M, Chaperon J, Edan G. Mitoxantrone as induction therapy in aggressive relapsing remitting multiple sclerosis: a descriptive analysis of 100 consecutive patients. *Rev Neurol (Paris)* 2006; 162: 185–194.
41. Rivera V, Al-Sabbagh A, Bennett R, et al. RENEW study update XVIII: ongoing evaluation of the safety and tolerability of mitoxantrone in worsening multiple sclerosis. *Mult Scler* 2008; 14: S175.
42. Hasan SK, Mays AN, Ottone T, et al. Molecular analysis of t(15;17) genomic breakpoints in secondary acute promyelocytic leukemia arising after treatment of multiple sclerosis. *Blood* 2008; 112: 3383–3390.