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V. Martinelli, E. Cocco, R. Capra, et al.

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V. Martinelli, MD
E. Cocco, MD
R. Capra, MD
G. Salemi, MD
P. Gallo, MD
M. Capobianco, MD
I. Pesci, MD
A. Ghezzi, MD
C. Pozzilli, MD
A. Lugaresi, MD
P. Bellantonio, MD
M.P. Amato, MD
L.M. Grimaldi, MD
M. Trojano, MD
G.L. Mancardi, MD
R. Bergamaschi, MD
C. Gasperini, MD
M. Rodegher, MD
L. Straffi, MD
M. Ponzio, PhD
G. Comi, MD
For The Italian Mitoxantrone Group

Address correspondence and reprint requests to Dr. Vittorio Martinelli, INSPE, S. Raffaele Institute, via Olgettina 48, 20132 Milan, Italy
martinelli.vittorio@hsr.it

ABSTRACT

Objectives: To evaluate the incidence and dose-dependency of mitoxantrone (MTX)-associated acute myelocytic leukemia (AML) in the network of Italian multiple sclerosis (MS) clinics.

Methods: We performed a multicenter retrospective cohort study of patients treated with MTX in MS centers under the Italian national health care system between 1998 and 2008. Demographic, disease, treatment, and follow-up information were collected using hospital records.

Results: Data were available for 3,220 patients (63% women) from 40 Italian centers. Follow-up (mean ± SD) was 49 ± 29 months (range 12–140 months). We observed 30 cases of AML (incidence 0.93% [95% confidence interval 0.60%–1.26%]). The mean cumulative dose was higher in patients with AML (78 vs 65 mg/m^2, $p = 0.028$). The median interval from the start of therapy to AML diagnosis was longer than expected at 33 months (range 13–84 months); 8 patients (27%) developed AML 4 years or more after the first MTX infusion. The rate of mortality associated with AML was 37%.

Conclusions: This higher than expected risk of AML and related mortality requires that treatment decisions must be made jointly between clinicians and patients who understand their prognosis, treatment options, and treatment-related risks. The now large exposed MS population must be monitored for hematologic abnormalities for at least 6 years from the end of therapy, to ensure the rapid actions needed for early diagnosis and treatment of AML. *Neurology*® 2011;77:1887–1895

GLOSSARY

AML = acute myelocytic leukemia; **APL** = acute promyelocytic leukemia; **CI** = confidence interval; **MS** = multiple sclerosis; **MTX** = mitoxantrone; **PML** = progressive multifocal leukoencephalopathy; **ROC** = receiver operating characteristic.

Mitoxantrone (MTX) is an anthracenedione derivative that intercalates into DNA, poisons topoisomerase II, and causes strand breaks that can result in chromosomal translocations.[1] Though originally developed as an antineoplastic, its immunosuppressive properties proved efficacious in managing multiple sclerosis (MS).[2,3]

Scattered reports of secondary leukemia led to restrictions on cumulative dose and a warning to monitor for adverse events.[4–11] In oncology, the use of topoisomerase II inhibitors had already been associated with a higher risk of secondary leukemia.[12] However, oncology patients are often exposed to more genotoxic stress than patients treated for MS and an early retrospective study of MTX in MS had revealed a low incidence of therapy-related acute myelocytic

From the Department of Neurology (V.M., M.R., L.S., G.C.), INSPE, San Raffaele Scientific Institute, Milan; Multiple Sclerosis Center (E.C.), Department of Cardiovascular and Neurological Science, University of Cagliari, Cagliari; Neuropsychology Unit (R.C.), Spedali Civili of Brescia, Brescia; Department of Clinical Neurosciences (G.S.), University of Palermo, Palermo; The Multiple Sclerosis Center of Veneto Region (P.G.), First Neurology Clinic, Department of Neurosciences, University Hospital of Padova, Padova; Neurologia 2-CRESM (M.C.), AOU S. Luigi, Orbassano; Multiple Sclerosis Centre (I.P.), Hospital of Fidenza, Fidenza; Neurological Unit (A.G.), Hospital of Gallarate, Gallarate; San Andrea Hospital (C.P.), La "Sapienza" Rome, Rome; Department of Neuroscience and Imaging (A.L.), University G. d'Annunzio, Chieti; Istituto Mediterraneo di Neuroscienze (P.B.), Pozzilli Isernia; Department of Neurology (M.P.A.), University of Florence, Florence; Fondazione Istituto San Raffaele "G. Giglio" Cefalu (L.M.G.), Cefalu; Department of Neurological and Psychiatric Sciences (M.T.), University of Bari, Bari; Department of Neurosciences (G.L.M.), Ophthalmology and Genetics, University of Genova, Genova; Multiple Sclerosis Center (R.B.), Neurological Institute C. Mondino of Pavia, Pavia; S Camillo-Forlanini Hospital (C.G.), Department of Neuroscience, Rome; and Department of Health Sciences (M.P.), Section of Medical Statistics and Epidemiology, University of Pavia, Pavia, Italy.

Coinvestigators are listed on the *Neurology*® Web site at www.neurology.org.

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Preliminary data from the present study were presented at the following international congresses: American Academy of Neurology annual meeting 2009; 19th World Congress of Neurology 2009; 25th Congress of the European Committee for Treatment and Research in Multiple Sclerosis 2009; 19th meeting of the European Neurological Society 2009.

Supplemental data at www.neurology.org

Supplemental Data

leukemia (AML).[13] Subsequent case and series reports have indicated that the incidence may be considerably higher.[14–21] The Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology recently conducted a systematic review of the evidence on the efficacy and safety of MTX, concluding that the incidence of treatment-related AML appears to be higher than previously thought, but that "comprehensive postmarketing surveillance data are lacking."[22] The entity of risk and the relationship between exposure and risk remain uncertain.

We have sought to resolve these questions by identifying a large cohort of patients with MS with well-defined exposure to MTX and determining how many of them had developed AML over time.

METHODS

Study design. In this retrospective cohort study, we collected data on a majority of Italian patients with MS treated with at least one infusion of MTX and observed for at least 1 year between 1998 and 2008. In Italy, patients with MS receive treatment within the network of MS centers registered with the Italian Health Authorities. A letter describing the study was sent to all MS centers in June 2007 and centers with experience treating at least 10 patients with MTX were invited to participate.

Participating centers were urged to identify and collect data on all patients treated during the study period. The following data were retrieved through review of the clinical databases at each center: demographic data, disease onset and clinical course, first and most recent MTX administrations, dosage, number of infusions, cumulative dose, and duration of follow-up. Detailed information on MS, cytogenetics, and previous therapies were requested for patients who developed leukemia.

Standard protocol approvals, registrations, and patient consents. The study was approved by the institutional review board of the San Raffaele Institute, Milan, who waived the requirement for informed consent due to the nature of the study.

Statistical analyses. The incidence rate of AML in patients with MS treated with MTX, as well as the incidence rate of death for patients who had AML, were determined using Poisson distribution. The duration of follow-up was calculated from the initiation of therapy to the last patient contact.

To identify factors that influence the risk of AML we analyzed differences in the occurrence of potential risk factors between patients who developed acute leukemia and patients who did not. We applied the Mann-Whitney *U* test for continuous variables and the Fisher exact test for categorical data. The results were described as mean and SD, median and interquartile range, or counts with percentages, where appropriate. Possible correlations between the diagnosis of AML and the cumulative dose of MTX or the interval from last infusion were assessed using Spearman rank correlation coefficients.

Variables that were found to be associated significantly with AML in univariate analyses were analyzed by multivariate Poisson regression, adjusting for potential confounding factors. These results were expressed as crude and adjusted rate ratios with 95% confidence intervals. To define the cutoff point of higher AML risk with cumulative dose of MTX, sensitivity and specificity were calculated as receiver operating characteristic (ROC) curves. The optimum was defined using the criteria of a balanced sensitivity and specificity and confirmed by Poisson regression with relative risk.

The study was approved by the Ethics Committee of the Coordinating Center (S. Raffaele Institute, Milan, Italy). Statis-

Table 1 Demographic and clinical patient characteristics

	MV, n (%)	No.	ALL	No.	AML (−)	No.	AML (+)	*p* Value
Patients	—		3,220		3,190	30	30	
Female, n (%)	—	3,220	2,044 (63)	3,190	2,028 (64)	30	16 (53)	0.246
Age, y, mean (SD)	69 (2.1)	3,151	44.2 (10.4)	3,121	44.2 (10.3)	30	44.0 (11.6)	0.748
MS course, n (%)	57 (1.8)	3,163		3,133		30		0.152
PP			186 (6)		184 (6)		2 (7)	
RR			1,411 (45)		1,393 (44)		18 (60)	
SP			1,566 (49)		1,556 (50)		10 (33)	
No. of cycles, n (%)	55 (1.7)	3,165		3,135		30		0.280
Min-max			1–24		1–24		1–16	
Median (IQR)			7 (5–10)		7 (5–10)		8.5 (6–11)	
Duration of treatment, mo, n (%)	36 (1.1)	3,184		3,154		30		0.437
Min-max			0.03–120.8		0.03–120.8		0.03–47.0	
Median (IQR)			14.7 (7–24)		14.7 (7–24)		17.0 (7–26)	
Cumulative dose, mg/m^2, n (%)	185 (6)	3,035		3,005		30		0.028
Min-max			5–144		5–144		12–130	
Median (IQR)			60 (40–90)		60 (40–90)		72 (60–108)	

Abbreviations: ALL = acute lymphoblastic leukemia; AML = acute myelocytic leukemia; IQR = interquartile range; MS = multiple sclerosis; MV = missing value; PP = primary progressive; RR = relapsing-remitting; SP = secondary progressive.

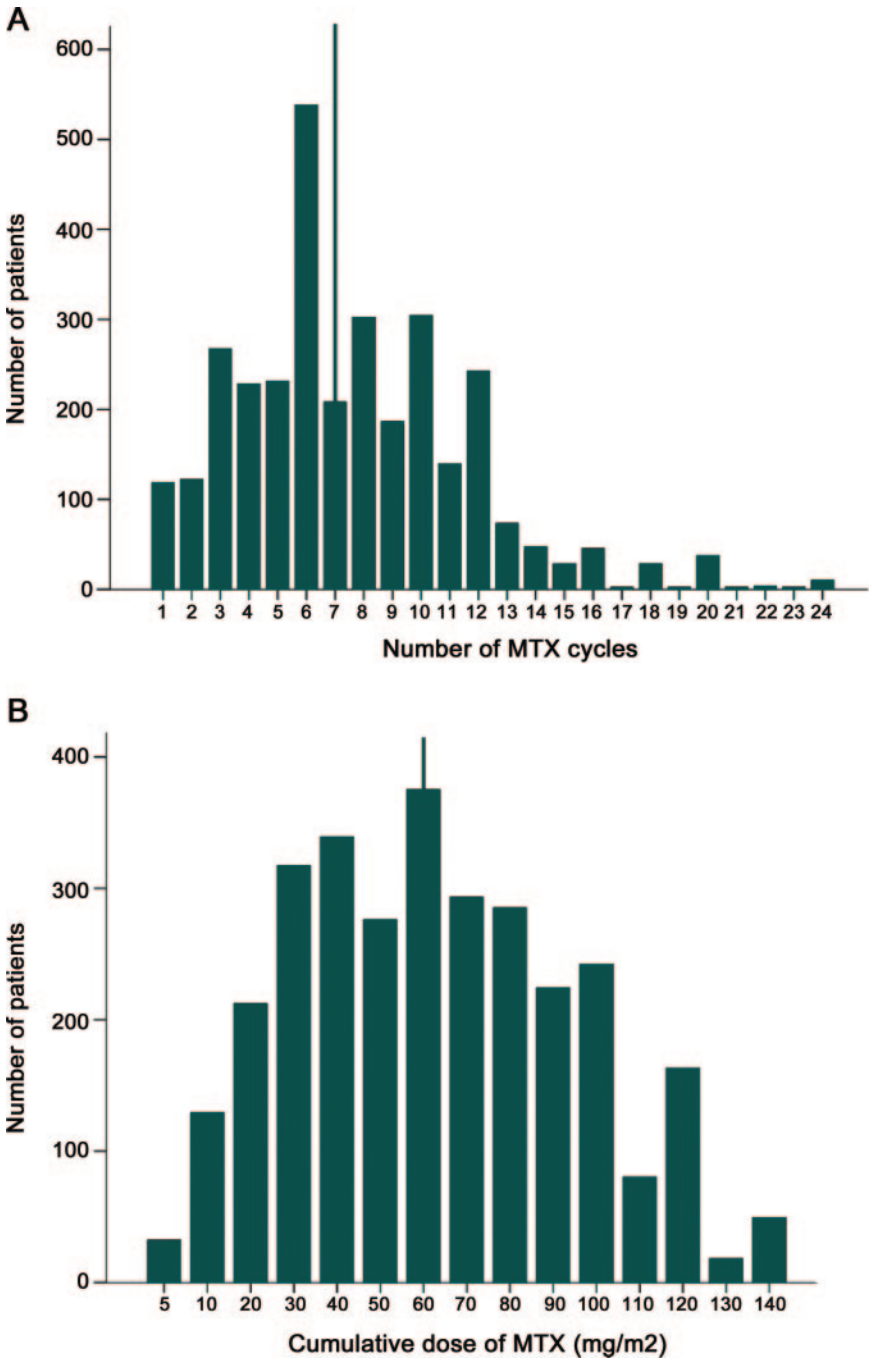
tical analyses were performed by M.P. using Stata statistical software, version 10 (StataCorp, College Station, TX).

RESULTS Forty centers, located throughout Italy, participated in this study. They represent 85%–90% of all patients treated with MTX in Italy during the study period.

By 2008, the 19 major Italian MS centers had managed approximately 30,000 patients with MS, 26,000 of whom were seen in the 16 major centers participating in this study (2 centers had not treated at least 10 patients and one had not prospectively collected data on all patients, making it impossible to determine the exact number of patients treated).

We collected data on 3,220 patients with MS treated with MTX; the 16 major MS centers contributed a median of 113 patients (range 63–539). The main clinical and demographic characteristics of the cohort are summarized in table 1.

Figure 1 Exposure to MTX treatment



(A) Distribution of the mitoxantrone (MTX) infusion number (mean number of infusions = 7.6). (B) Distribution of single patient cumulative dose of MTX (patients' mean cumulative dose = 64.8 mg/m^2).

Various dosage regimens were used, with MTX administered about monthly in 940 patients, every 2 months in 1,280 patients, every 3 months in 684 patients, and at intervals of 4 or more months in 183 patients. A regular administration pattern was not observed in 133 patients. The mean number of MTX administrations was 7.6 and the mean cumulative dose was 64.8 mg/m^2 (figure 1, A and B). Sixty-two percent of patients received a cumulative dose between 30 and 89 mg/m^2. The cumulative doses administered to patients who developed AML are presented in table 2. Follow-up (mean ± SD) was 48.3 ± 28.3 months (range 12–140); only 779 patients were observed for less than 24 months.

We observed 30 cases of AML (table 2). Acute promyelocytic leukemia (APL) was the most frequently reported AML subtype (19 cases), representing 76% of the patients with defined subtypes. One case each of chronic myeloid leukemia and acute lymphoblastic leukemia were recorded but not included in evaluations because they are not considered to be treatment-related. The incidence of AML was 0.93% (95% confidence interval [CI] 0.60%–1.26%), which represents a global risk of 1 case per

Table 2 Demographic and clinical characteristics of the patients who developed AML

Sex	MS	Cumulative dose, mg/m^2	Age at start of MTX therapy, y	Interval from start of therapy to AML diagnosis, mo	Type of AML[a]	Leukemia outcome so far
M	RR	12	24	13	M3	Remission
F	SP	22.5	56	36	M3	Remission
F	RR	24	28	28	M3	Remission
F	RR	30	46	16	M3	Remission
M	SP	45	30	36	M3	Remission
F	SP	48	50	63	Not stated	Death
M	RR	50	60	39	Not stated	Death
F	RR	60	43	35	M3	Death
M	SP	60	35	56	M3	Death
F	RR	60	23	25	M4	Remission
M	SP	60	44	24	Not stated	Death
F	SP	60	35	39	M3	Remission
M	PP	71	37	20	M3	Remission
M	SP	72	48	31	M3	Remission
F	PP	72	61	20	M3	Death
F	RR	72	28	84	M3	Remission
M	RR	90	25	47	M3	Death
F	RR	95	33	25	M4	Remission
M	SP	96	52	31	Not stated	Death
M	RR	96	32	26	Not stated	Death
F	RR	100	34	35	M3	Remission
F	RR	100	24	32	M3	Remission
F	RR	108	27	36	M2	Death
M	RR	110	37	22	M3	Remission
F	RR	110	59	68	M5	Remission
M	SP	110	58	45	M3	Remission
M	RR	120	46	28	M3	Remission
M	SP	120	58	49	M7	Death
F	RR	130	55	50	M3	Remission
F	RR	130	47	40	M4	Remission

Abbreviations: AML = acute myelocytic leukemia; MS = multiple sclerosis; MTX = mitoxantrone; PP = primary progressive; RR = relapsing-remitting; SP = secondary progressive.
[a] AML subtypes according to the French-American-British Classification (M2 acute myeloblastic leukemia; M3 acute promyelocytic leukemia; M4 acute myelomonocytic leukemia; M5 acute monoblastic leukemia; M7 acute megakaryoblastic leukemia).

Figure 2 Box plot of cumulative dose of mitoxantrone (MTX) for patients with (+) and without (−) acute myelocytic leukemia (AML)

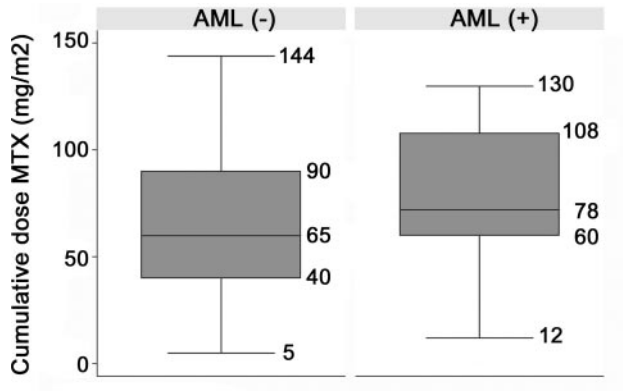


Table 3 Crude and adjusted rate ratio of AML cases in patients with MS

Cumulative dose	Unadjusted RR (95% CI)[a]	Adjusted RR (95% CI)[b]
>60 mg/m^2	1.55 (0.69–3.48)	2.30 (0.86–6.17)
>72 mg/m^2	1.40 (0.68–2.88)	2.16 (0.83–5.65)
>108 mg/m^2	2.33 (1.04–5.24)	4.89 (1.64–14.63)

Abbreviations: AML = acute myelocytic leukemia; CI = confidence interval; MS = multiple sclerosis; RR = rate ratio.
[a] Poisson regression model.
[b] Poisson regression model adjusted for duration of treatment and number of cycles.

107 MTX-treated patients. We estimated an AML incidence rate of 0.19 (95% CI 0.14–0.28) per 1,000 person-months. Four of the patients who developed AML had been treated previously with immunosuppressive drugs (3 with azathioprine and 1 with cyclophosphamide). All others had received first-line immunomodulating therapy. The median interval from the start of MTX therapy to the diagnosis of AML was 33.3 months (range 13.3–84.2 months; interquartile range 24.6–40.3).

Patients who developed AML had received a higher mean cumulative dose of MTX than patients who did not (78 vs 65 mg/m^2, $p = 0.028$), suggesting a relationship between cumulative dose and the development of AML (figure 2). Using cumulative dose as the exposure factor and adjusting for the duration of treatment and number of cycles, we observed a rate ratio of 1.03 (95% CI 1.01–1.06, $p = 0.005$). In other words, there was a 3% increase in the risk of AML for every one unit increase in cumulative dose. We then categorized cumulative dose using quartiles based on the 25th, 50th, and 75th percentiles of the cumulative doses received by patients who developed AML and calculated the crude and adjusted rate ratio for each category. An excess risk of AML was observed for all 3 dose categories analyzed (table 3). The rate ratio adjusted for duration of treatment and number of cycles was higher, but the level of significance was similar. We observed a higher risk of AML (rate ratio = 4.89, $p = 0.004$) in patients who had a cumulative MTX dose >108 mg/m^2. Using ROC analysis, we identified a cumulative dose of 90 mg/m^2 as the cutoff point best associated with higher AML risk (sensitivity 47%, specificity 75%). The Poisson regression demonstrated that patients with cumulative doses higher than 90 mg/m^2 had a risk ratio of 3.44 (95% CI 0.92–3.87, $p = 0.014$).

No significant difference was observed between MTX-treated patients who developed or did not develop AML regarding gender, age, disease course, number of infusions, individual infusion dose, or duration of treatment.

At this writing, 11 of the 30 patients who developed AML have died (mortality rate 36.7%) with a corresponding mortality incidence rate of 1.09 (95% CI 0.58–2.02) per 100 cases of AML-month. Six patients (20%) died before any diagnostic workup or induction therapy. The median survival time was 31 months. We estimated an incidence rate of death due to AML of 0.07 (95% CI 0.04–0.13) per 1,000 person-months treated with MTX. No significant difference was observed in leukemia outcome when patients were analyzed on the basis of cumulative MTX dose ($p = 0.793$), number of infusions ($p = 0.229$), duration of MTX treatment ($p = 0.401$), age ($p = 0.254$), or AML subtype ($p = 0.190$).

DISCUSSION Our main finding is a high incidence of AML in Italian patients with MS treated with MTX. Our results strongly support that the risk of AML in MTX-treated patients with MS is similar to that associated with the use of topoisomerase II inhibitors in the oncology setting.[23]

The high incidence of AML observed in our MTX-treated cohort of patients is significantly higher than the average incidence (about 1:1,000) observed in the Italian general population with age lower than 64 years (Italian Network of Cancer Registries, 1998–2002). This finding contrasts with the absence of treatment-related leukemia in the early studies that supported the regulatory approval of MTX for this indication,[2,3] however, this may be due to the relatively small group sizes and short durations of these studies, which were directed primarily at establishing efficacy and not adequately powered to detect rare adverse drug reactions. Subsequently, much

higher cumulative incidences were found in a number of relatively small case series.[19,20] Our findings also contrast with those of a recently concluded phase IV postmarketing surveillance study.[24]

Estimates of the incidence of treatment-related AML after therapy with MTX vary considerably. A meta-analysis of data from 15 large case series recent showed a 3-year MTX-related leukemia incidence of 0.33% in 5,472 MTX-treated patients with MS.[20] Although lower than our finding, their estimate of the risk of acute leukemia (1:333) represents a significant increase over the risk for the general population. Meanwhile, a long-term prospective study observed 230 MTX-treated patients with MS for a mean of nearly 5 years from start of therapy, identifying 5 cases of AML and an incidence of 2.2%.[19] Our data, obtained after a mean follow-up of 4 years from the start of therapy, indicate a risk intermediate between these reports and in agreement with an estimated incidence of 0.81% from a recent analysis of all published data for which a denominator was available, regardless of length of follow-up.[22] At least part of the difference in incidence among these studies may be attributed to variation in the length of observation; however, contributions from different treatment regimens (e.g., combination with methylprednisolone), and population-level differences in genetic factors influencing DNA repair, drug metabolism, or susceptibility to AML itself, must be taken into account.[25]

While we did not identify independent patient characteristics that affected AML risk, it is important to point out that we did not collect data on health behaviors, lifestyle, or comorbidities. For example, smoking is a weak risk factor for AML that causes a 30% increase in AML risk (smokers vs lifelong nonsmokers).[26] When we designed this study the incidence of AML in Italian patients treated with MTX was not known and we decided to focus on "essential" data addressing this question. We sought to reduce the collection burden on participating centers in hope of obtaining maximum participation in the absence of financial support, albeit at a cost of less detailed information on individual patients. A case-control study on all MTX-treated patients with MS should be planned to investigate cofactors potentially able to influence cancer risk.

Data from several large MS cohorts reveal a reduction in the risk of several cancers in untreated patients with MS.[27,28] Moreover, none of these large population-based studies report a significant increase in "hematopoietic or lymphatic" malignancies among patients with MS. The cumulative risk of AML in the Italian general population below the age of 64 years is approximately 9 times less than the incidence we observed in MTX-treated patients. This difference would be even greater if, for instance, heightened immune surveillance in untreated patients with MS resulted in a lower incidence of AML.

The first reported MTX-related acute leukemia manifested after 5 years,[5] and, while this has been described as an outlier,[22] our results suggest that late onset of AML may be more frequent than previously thought. Therefore monitoring for hematologic abnormalities related to acute leukemia should continue for 6 years from the end of MTX exposure. At this writing, only about half of our patients have been observed for 5 years and additional cases are likely to develop.

The second major question was whether the risk of developing AML is dose-dependent. Our findings indicate that the frequency of AML increases progressively in patients who received higher cumulative doses of MTX, confirming a recent report.[20] This has important implications for therapy and, although it is not possible to establish a safe cumulative dose, based on current information, a reasonable cumulative dose might be 30–60 mg/m^2 administered as part of a therapeutic strategy to reduce exposure to MTX.

One such strategy is a sequential treatment regimen that employs short-term MTX induction therapy followed by maintenance therapy with a better tolerated immunomodulating therapy. In theory, this approach takes advantage of a powerful immunosuppressant to "reset" the immune system, resulting in the replacement of proinflammatory cells with anti-inflammatory cells.[29] Initial evaluations have shown that this strategy is efficacious,[29] but the number of patients treated to date do not permit a rigorous analysis of safety. Based on available data, a low MTX cumulative dose would be expected to have a lower, but ever-present risk of therapy-related leukemia and therefore still warrant long-term surveillance.

The impact of our findings on clinical practice should be to require a careful evaluation of treatment options by clinicians together with each candidate for therapy, in light of prognostic clinical and MRI parameters. The potential benefits of MTX treatment in preventing progressive irreversible disability from MS must be balanced against the risk of treatment-related mortality from cardiotoxicity and secondary leukemia. We should consider not only the higher incidence of therapy-related leukemia with MTX, but also the mortality rate associated with it. Alternative therapies and their associated risks should also be considered. The anti-integrin α4 monoclonal natalizumab, also approved for this indication, has an associated risk of mortality from progressive multifocal leukoencephalopathy (PML) of 0.3 per 1,000 patients.[30]

The attitudes of a large group of patients with MS toward assuming the risk of life-threatening treatment-related effects in return for better MS outcomes were assessed recently with a survey questionnaire.[31] It was revealed that patient concerns center mainly on mortality from therapy-related adverse events, rather than the adverse events themselves.

It is also necessary that the estimated tens of thousands of patients exposed to MTX over the past 6 years be closely monitored for adverse hematologic events. AML usually progresses rapidly and may be fatal within days or weeks if untreated. A serious warning comes from the fact that 6 out of 11 patients died before any initial workup or induction therapy. Early detection of hematologic abnormalities related to an incipient acute leukemia is crucial to preventing dramatic and fatal evolution of the disease. Suspected leukemia should be managed as a medical emergency. Current treatment strategies provide excellent therapeutic results in the management of AML,[32] particularly APL.[33]

The retrospective manner in which our data were collected could represent a limitation, since an indefinable number of patients who received MTX may not have been included in the denominator; however, we believe that this had a limited impact on our analysis. We would argue that the well-organized network of MS centers under the Italian National Health System, the systematic recording of information in databases, and the requirement that patients present at registered centers for treatment and follow-up has allowed us to identify nearly 90% of the exposed population. We must also keep in mind that, at this writing, only about half of the Italian patients have had 5 years of follow-up and additional patients are likely to develop AML in the coming months or years. Likewise, this close association of Italian MS centers and the severity of AML make it unlikely that a case of AML would go unreported. On the contrary, the published prospective studies have had ≥10% loss of patients from death or loss to follow-up, leading to the possibility that patients who developed AML were not identified.[24,34]

Finally, 10 years are usually necessary to define the efficacy and the short-term side effects of a new drug before it reaches the market, but it has taken another 10 years of comprehensive postmarketing surveillance to appreciate the true incidence of severe and life-threatening side effects related to MTX. The MTX "lesson" must represent a warning for emerging therapies that comprehensive, thorough, and long-term postmarketing surveillance must be carried out in each country and lead to periodic reanalysis of the global risk/benefit ratio. In the future, only the combined effort and collaboration of pharmaceutical companies, drug regulatory agencies, and clinical practitioners will be able to ensure timely solutions. Nevertheless it could be that the latter are best suited, if not the best equipped, to be entrusted with the task of active long-term surveillance in the real-world setting, with the goal of moving toward an innovative postmarketing drug safety model.[35] Investment in informatics infrastructure and systematic data collection systems that integrate also information from national health care databases and census information would help to overcome the limitations of voluntary reporting and could be one solution to this challenge.

AUTHOR CONTRIBUTIONS

Dr. Martinelli: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, study supervision. Dr. Cocco: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Capra: drafting/revising the manuscript, acquisition of data. Dr. Salemi: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Gallo: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Capobianco: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Pesci: drafting/revising the manuscript, contribution of vital reagents/tools/patients. Dr. Ghezzi: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Pozzilli: drafting/revising the manuscript. Dr. Lugaresi: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Bellantonio: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data. Dr. Amato: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Grimaldi: drafting/revising the manuscript, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Dr. Trojano: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Mancardi: analysis or interpretation of data, acquisition of data. Dr. Bergamaschi: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis. Dr. Gasperini: drafting/revising the manuscript, acquisition of data. Dr. Rodegher: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. Dr. Straffi: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Ponzio: analysis or interpretation of data, statistical analysis. Dr. Comi: drafting/revising the manuscript, study supervision.

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DISCLOSURE

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