Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis

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ABSTRACT

We report the clinical features and treatment outcome of 33 patients with multiple sclerosis who developed acute promyelocytic leukemia. Thirty patients were previously exposed to mitoxantrone. The median latency period between treatment initiation and acute promyelocytic leukemia diagnosis was 32 months. The *PML-RARA* bcr1 isoform was identified in 87% of cases. Twenty-nine (90%) patients achieved hematologic remission after all-trans retinoic acid and chemotherapy (n=31) or arsenic trioxide and all-trans retinoic acid. Consolidation included modified chemotherapy or arsenic trioxide. At a median follow up of 26 months, 23 patients are in complete remission, 4 relapsed and one developed secondary leukemia. The 5-year cumulative incidence of relapse and overall survival were 23% and 68%, respectively. Although treatment heterogeneity and suboptimal post-remission therapy must be taken into account, overall results and development of secondary leukemia in one patient suggest that effective and less toxic agents like arsenic trioxide warrants further investigation in this context.

Key words: acute promyelocytic leukemia, secondary leukemia, multiple sclerosis.

Citation: Ammatuna E, Montesinos P, Hasan SK, Ramadan SM, Esteve J, Hubmann M, Pagoni M, Grimwade D, Sanz MA, and Lo-Coco F. Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis. Haematologica 2011;96(4):621-625. doi:10.3324/haematol.2010.036657

Introduction

Secondary acute promyelocytic leukemia (APL) has been frequently reported as a late complication of chemotherapy (therapy-related APL [t-APL]).[1-3] Topoisomerase II (topo-II) inhibitors such as mitoxantrone (MTZ), epirubicin, adriamycin, and etoposide are the chemotherapy compounds most frequently associated with development of t-APL by inducing DNA double strand breaks.[4-6] Among them, MTZ is the most commonly implicated agent.[5,6] The latency between exposure to topo-II inhibitors and the development of t-APL is relatively short (< 3 years) and t-APL typically occurs without an antecedent myelodysplastic phase.[3,4] Although t-APL developing after chemotherapy for a primary cancer has been reported frequently, only a few cases of t-APL arising after treatment of non-malignant diseases have been described so far. In the past few years, however, an increasing number of reports on t-APL occurring after multiple sclerosis (MS) have been published.[5,6]

MS is a chronic autoimmune demyelinating disease of the central nervous system characterized by variable periods of relapse and remission of neurological symptoms and progression of disability over time. MTZ was the first immunosuppressive drug approved in the US and Europe as a single agent for treatment of relapsing-remitting (RRMS) or progressive MS.[7] We recently investigated at the genomic level the location of DNA breakpoints in t-APL arising after MS. Interestingly, this analysis revealed a distinct distribution of chromosome 15 breakpoints as compared to *de novo* APL, biased towards disruption of chromosome 15 breakpoints within *PML* intron 6. Moreover, we reported that breakpoints in MTZ-treated cases fell at high frequency within an 8-bp region corresponding to a previously described "hotspot" identified in t-APL arising after treatment of breast cancer with regimens containing anthracyclines.[8,9]

In the present study, we report on the presenting features and treatment outcome of 33 patients who developed APL on a background of MS, including 30 who received MTZ for their primary disease.

Design and Methods

A call for studying t-APL cases was started in 2008 in the Italian GIMEMA group and extended subsequently to several European cen-

Acknowledgments: we are indebted to to Drs. Chiara Cattaneo, Antonio Ledda, Enrico Montefusco, Francesco Di Raimondo, Mariaenza Mitra, Maria Teresa Lupo Stanghellini, Maria Teresa Voso, Lorella Melillo, Richard Schlenk, Wolgang Sperr and Paolo Bernasconi who contributed some of the patient data for the present study.
Funding: this work was partially supported by Associazione Italiana per la Ricerca sul Cancro (AIRC).
Manuscript received on October 29, 2010. Revised version arrived on December 13, 2010. Manuscript accepted on December 21, 2010.
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ters. This study initially included the characterization at the genomic level of "hotspot" breakpoints in both *PML* and *RARA* genes. Genomic studies of *PML* and *RARA* of 23 out of 33 patients included in the present series have been reported in two separate articles,[8,9] while the clinical features and outcome of 14 of 33 patients have been included in one of these previous reports.[8] MS patients received therapy according to the disease form as indicated.[7] The diagnosis of t-APL was confirmed in all cases by reverse-transcriptase polymerase chain reaction (RT-PCR) or FISH detection of the *PML-RARA* hybrid gene.[10] *FLT3* mutation screening for internal tandem duplications (ITD) was carried out as described.[11] APL was treated in all but one case with ATRA and anthracycline based combination chemotherapy induction according to treatment protocols active in various countries.[12-16] These protocols included the AIDA 2000 of the Italian GIMEMA study group,[12] the PETHEMA LPA2005,[13] and the PETHEMA LPA 99,[14] UK MRC AML15[15] and the German AMLCG.[16] All protocols received approval from the corresponding IRB and/or ethical committees. Patients were enrolled in the respective trials prospectively and were treated accordingly after signing informed consent. One patient (UPN 18) was treated without chemotherapy during induction, as detailed below (*see Results and Discussion*).

Unadjusted time-to-event analyses were performed using the Kaplan-Meier estimate.[17] The probability of relapse was also estimated by the cumulative incidence method (for marginal probability).[18,19] Overall survival (OS) was calculated from the date of starting induction therapy, while cumulative incidence of relapse (CIR) was calculated from the date of CR.[20] For CIR analysis, death in CR and development of secondary leukemia were considered as a competing cause of failure.[18,19] For all estimates in which the event "relapse" was considered as an end point, hematologic and molecular relapse, as well as molecular persistence at the end of consol-

Table 1. Clinical characteristics of 33 patients with MS.

UPN	Sex	Age at MS diagnosis	Type of MS	MS therapy	Total MTZ dose (mg)	Latency between MS and t-APL	Latency between MTZ and t-APL
1	F	62	SPMS	MTZ – Azathioprine –INFb	60	13	10
2	F	52	SPMS	MTZ	35	192	37
3	F	56	PPMS	PDN – MTZ	70	30	4
4	F	24	RRMS	MTZ	147	150	6
5	F	21	RRMS	MTZ	170	66	18
6	F	53	RRMS	MTZ	234	72	51
7	F	25	RRMS	MTZ	110	37	27
8	M	44	SPMS	MTZ	100	29	29
9	M	32	PPMS	MTZ	176	30	30
10	M	26	RRMS	INFb	NA	NA	NA
11	F	29	RRMS	MTZ	81	97	17
12	M	50	RRMS	PDN	NA	216	NA
13	M	40	PPMS	MTZ	64	120	60
14	F	25	SPMS	MTZ	120	237	34
15	F	23	SPMS	MTZ	195	135	76
16	F	41	RRMS	MTZ	40	42	30
17	F	27	RRMS	MTZ	39	36	26
18	F	26	RRMS	MTZ	95	29	17
19	M	UNK	UNK	MTZ	UNK	UNK	UNK
20	F	35	SPMS	MPDN – MTZ - Copaxone	105	96	41
21	M	UNK	UNK	MTZ	162	UNK	48
22	F	34	SPMS	MPDN – MTZ	114	180	19
23	F	UNK	UNK	MTZ	95	UNK	UNK
24	F	34	UNK	MTZ	180	144	36
25	M	35	RRMS	MPDN – IFNb - Azathioprine	NA	84	NA
26	M	19	RRMS	PDN – MTZ – INFb - Azathioprine	90	86	36
27	M	25	RRMS	MTZ - INFb	14	24	24
28	F	40	PPMS	MTZ	200	46	34
29	M	50	RRMS	IFNb-MTZ - Copaxone	120	276	35
30	F	44	RRMS	IFNb-MTZ -Natalizumab	220	28	25
31	F	27	UNK	IFNb-MTZ - Copaxone	UNK	228	UNK
32	M	UNK	SPMS	MTZ	242	72	33
33	F	UNK	RRMS	MTZ	133	78	42

UPN: unique patient number; PDN: prednisone; MPDN: methylprednisolone; MTZ: mitoxantrone; INFb: interferone beta; UNK: unknown; NA: not applicable. RRMS, relapsing-remitting multiple sclerosis; SPMS, secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis.

idation were each considered as uncensored events.[20] Computations were performed using the 3D, 4F, 1L, and 2L programs from the BMDP statistical library (BMDP Statistical Software, Los Angeles, CA, USA), and R 2.7.2 software package for CIR and Fine and Gray model.

Results and Discussion

Thirty-three patients with APL developed after MS are included in the study. Patient data were collected retrospectively from Italy (n=14), Spain (n=10), UK (n=3), Germany (n=3), Greece (n=2), and Austria (n=1) as summarized in Table 1. Detailed information about the type of primary disease (MS) was available for 28 patients. MS was categorized as relapsing-remitting disease (n=16), secondary progressive (n=8) and primary progressive (n=4). Thirty out of 33 patients were treated with MTZ for their primary disease and 21 of them were exposed to MTZ only, while 9 patients received more than one immunosuppressive agent. Three patients were not exposed to MTZ and received other treatments including steroids (UPN 12), interferon-beta (UPN 10) and sequential steroids, interferon-beta and azathioprine (UPN 25). The median latency period between MS diagnosis and occurrence of APL was 91 months (range 18-336 months). MTZ doses were available for 28 patients with a median cumulative dose of 112 mg MTZ (range 14-242 mg). Median time elapsed between the first exposure to MTZ and APL diagnosis was 32 months (range 4-76 months).

Data related to APL presenting features are summarized in Table 2. The *PML-RARA* transcript type was available in 30 cases. Twenty-six (87%) patients had bcr1 (or "long" isoform) and 4 (13%) the bcr3 (or "short") transcript (Table 1). One patient showed concomitant rearrangements of the *BCR-ABL* and *PML-RARA* genes in leukemic cells, as shown by FISH analysis and RT-PCR. The results for *FLT3* ITD mutational analysis at diagnosis were available for 19 patients and showed this alteration in 3 of them (16%).

After APL diagnosis, one patient died of cerebral hemorrhage on day 1 prior to receiving any treatment. Three patients died during induction because of infection, differentiation syndrome, and CNS bleeding, respectively. Of the evaluable 29 patients in CR after induction, 21 received the planned consolidation cycles according to the previously mentioned protocols,[12-16] 7 patients (6 in the GIMEMA AIDA-2000 and one in the German AML trials) received modified consolidation therapy deviating from planned protocols and one patient died after first consolidation due to infection. As to patients receiving modified consolidation, 3 (UPN 4, UPN 5 and UPN 17) received idarubicin 5mg/m^2 for four consecutive days during the second course of consolidation replacing MTZ and 3 patients (UPN 28, UPN 30 and UPN 32) received consolidation with ATO and ATRA. UPN 33 enrolled in the German trial AMLCG received cytarabine and ATRA for consolidation together with one patient (UPN 18) who was not enrolled in any of these protocols.

All 28 evaluable patients achieved molecular remission after consolidation and 20 of them received some type of maintenance as detailed in Table 3. After a median follow up of 26 months (range 3-82 months), 23 patients are in continuous complete remission (CCR) at a median time of 23 months (range 2-82), while 4 patients (14%) relapsed at a median time of 29 months (range 26-31). One patient (UPN 8) developed sAML with 11q23 rearrangement two years after achieving CR. The 5-year OS and CIR rates were 68% and 23%, respectively (Figure 1A and B).

Compared to *de novo* APL, among our patients there was a predominance of females with a female/male ratio of 1.75. This finding most likely reflects the higher frequency of MS in females. As to the biological characteristics, compared to *de novo* APL[12,21] we found in this series a skewed distribution of *PML-RARA* isoforms with increased frequency of the bcr1 type. We believe that this finding might be correlated with the reported "hotspot" present in the *PML* gene intron 6 that appears to be more susceptible to MTZ-induced DNA breakpoints.[7,8] Concerning other molecular lesions hereby analyzed, the frequency of *FLT3-ITD* was slightly inferior in MS-tAPL as compared to *de novo* APL.

t-APL typically occurs without an antecedent myelodysplastic phase and after a relatively short (< 3 years) latency period from exposure to topo-II inhibitors.[3,4] Only a few cases of t-APL arising after treatment of non-malignant diseases and in particular after MS have been described so far.[5,6] Median time elapsed between the first exposure to MTZ and APL diagnosis was 32 months (range 4-76 months), in keeping with latency reported for t-APL occurring after a primary tumor.[1-3]

With respect to treatment outcome, we observe that OS in this series was slightly inferior to that reported for *de novo* APL patients receiving current standard therapy.[12,13] However, patients in this study were collected from several European countries and were not homogeneously treated, particularly as concerns the post-induction phase (Table 3). In particular, also in the light of elevated MTZ

Table 2. Demographic and clinical-biological characteristics of 33 patients with MS-tAPL.

	t-APL secondary to MS
Male patients, n (%)	12/33 (36)
Median age (range)	43 (23-68)
MS diagnosis, n (%):	
PPMS	4 (12)
RRMS	17 (52)
SPMS	8 (24)
NA	4 (12)
Median cumulative dose of MTZ (range)	112 mg (14-242)
Median latency between MS and APL diagnosis (range)	91 months (18-336)
Median time between the first exposure to MTZ and APL diagnosis (range)	32 months (4-76)
WBC×10^9/L median (range)	3 (0.4 -72)
Plt×10^9/L median (range)	25 (4- 90)
PML-RARa isoforms	
bcr1	26 (87)
bcr2	0
bcr3	4 (13)
Relapse-risk group, n (%)	
Low	9 (29)
Intermediate	15 (48)
High	7(23)

NA: not available; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis; PPMS: primary progressive multiple sclerosis; MTZ: mitoxantrone.

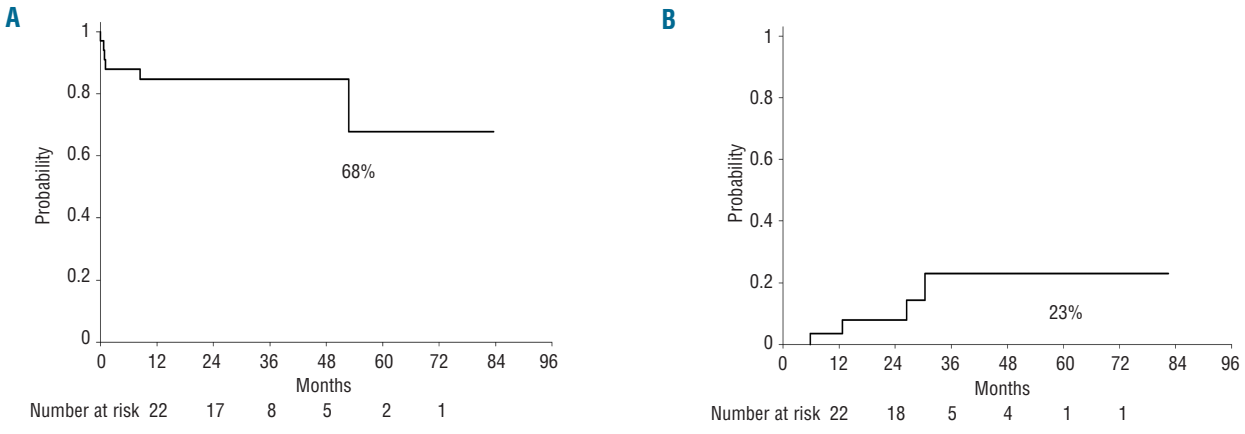

Figure 1. (A) Kaplan-Meier estimate for overall survival in 33 patients with MS-tAPL. (B) Kaplan-Meier estimate for cumulative incidence of relapse in 33 patients with MS-tAPL.

Table 3. Treatment details and response in 33 patients with MS-tAPL .

UPN	Sanz risk score	bcr type	APL induction	APL consolidation	APL maintenance	Status/last follow-up (months)
1	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	NA	Died
2	Low	1	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	CCR (41)
3	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (35)
4	Low	1	GIMEMA AIDA 2000	AIDA 2000 without MTZ	No maintenance (Auto –BMT)	CCR (54)
5	Intermediate	1	GIMEMA AIDA 2000	AIDA 2000 without MTZ	No maintenance (Auto –BMT)	CCR (54)
6	Low	1	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	CCR (35)
7	Intermediate	1	UK MRC	UK MRC	No maintenance*	Relapsed
8	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	No maintenance	t-AML
9	High	1	GIMEMA AIDA 2000	AIDA 2000	No maintenance	CCR (26)
10	High	3	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	Relapsed
11	Low	1	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	CCR (30)
12	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (17)
13	Intermediate	3	NA	NA	NA	Died
14	High	1	PETHEMA APL 2005	PETHEMA APL 2005	No maintenance	CCR (28)
15	Intermediate	1	GIMEMA AIDA 2000	AIDA 2000 without MTZ	AIDA 2000	CCR (26)
16	Intermediate	1	GIMEMA AIDA 2000	NA	NA	Died
17	High	3	GIMEMA AIDA 2000	ATO – ATRA	No maintenance	CCR (7)
18	High	1	ATO-ATRA based prot.	Cytarabine + ATRA	ATRA only	CCR (9)
19	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (24)
20	Low	1	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (6)
21	Intermediate	1	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (12)
22	High	UNK	PETHEMA APL 2005	NA	NA	Died
23	Low	UNK	PETHEMA APL 2005	PETHEMA APL 2005	PETHEMA APL 2005	CCR (11)
24	Low	3	PETHEMA APL 2005	NA	NA	Died
25	Intermediate	1	PETHEMA APL 1999	PETHEMA APL 1999	PETHEMA APL 1999	CCR(82)
26	Intermediate	UNK	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	CCR (23)
27	Low	1	GIMEMA AIDA 2000	AIDA 2000	AIDA 2000	CCR (19)
28	Intermediate	1	GIMEMA AIDA 2000	ATO+ATRA	No maintenance	Relapsed
29	High	1	GIMEMA AIDA 2000	AIDA 2000	ATRA only	Relapsed
30	Intermediate	1	GIMEMA AIDA 2000	ATO +ATRA	AIDA 2000	CCR (8)
31	Low	1	GIMEMA AIDA 2000	AIDA 2000	No maintenance	CCR (2)
32	High	1	GERMAN AMLCG	ATO + ATRA	No maintenance	CCR (8)
33	Intermediate	1	GERMAN AMLCG	Cytarabine + ATRA	GERMAN AMLCG	CCR (7)

*CCR: continuous complete remission. NA: not applicable UNK: unknown, MTZ: mitoxantrone, ATO: arsenic trioxide, ATRA: all trans retinoic acid. * No maintenance according to protocol.*

cumulative doses previously given for MS, some investigators elected to decrease the amount of post-induction chemotherapy by omitting or substituting MTZ in consolidation. In fact, 2 of the 4 patients who relapsed did not receive anthracyclines in consolidation (UPN 28) or in maintenance (UPN 29) while the third patient (UPN 7) did not receive any maintenance based on the study protocol. Due to this level of heterogeneity and to the limited number of patients in this series, it is difficult to draw firm conclusions on the optimal treatment for MS-tAPL. However, the occurrence of 3 deaths due to treatment-related toxicity (including one in CR) and of one case of secondary AML may raise concerns on excessive exposure to chemotherapy and in particular to MTZ.

Recently, the PETHEMA group reported a cumulative incidence of sAML of 2.2% at six years for patients with *de novo* APL treated with standard ATRA and anthracycline-based chemotherapy.[21] In addition, the outcome of patients with t-APL after ATO containing front-line therapy was found to be comparable to conventional induction therapy containing anthracyclines.[22] It seems, therefore, reasonable, at least in the post-induction phase, to suggest the use of effective agents with different toxicity profile such as ATO for this particular subset of t-APLs, as well as for those APL cases which developed after a primary cancer treated with chemotherapy.

Authorship and Disclosures

The information provided by the authors about contributions from persons listed as authors and in acknowledgments is available with the full text of this paper at www.haematologica.org.

Financial and other disclosures provided by the authors using the ICMJE (www.icmje.org) Uniform Format for Disclosure of Competing Interests are also available at www.haematologica.org.

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