Acta neurol. belg., 2008, **108**, 99-102

Case reports

Mitoxantrone-related acute leukemia in two MS patients

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Abstract

We report two new cases of mitoxantrone-related leukemia occurring in two patients with multiple sclerosis (MS), 14 and 18 months after the last infusion of the drug. One patient was successfully treated. We were able to collect 29 other cases in the literature. Most of them were single reports but some were described within cohorts of mitoxantrone-treated MS patients. The incidence rate was 0.65% from all cohorts totalizing 2299 patients. Acute promyelocytic leukemia with the translocation t(15;17) was over-represented in the MS population in comparison with cancer patients also treated with mitoxanrone. The occurrence of leukemia was dose-independent and appeared with a mean delay of 20 months after the end of the treatment.

Key words : Multiple sclerosis ; mitoxantrone ; leukemia ; immunosuppression.

Introduction

Mitoxantrone is an anthracenedione agent approved for the treatment of patients with worsening MS. Its use requires careful monitoring for potential adverse effects, especially because of heart toxicity (Goffette *et al.*, 2005). In addition, mitoxantrone causes topoisomerase II inhibition which impairs DNA repair mechanisms. Topoisomerase II inhibitors are associated with characteristic toxic acute leukemia with short latency, absence of a myelodysplastic phase, and balanced chromosomal aberrations. Mitoxantrone has been especially implicated in the translocation t(15;17), which is the hallmark of acute promyelocytic leukemia (APL), also called M3 in the French-American-British (FAB) classification (Mistry *et al.*, 2005) We report two new cases of mitoxantrone-related acute leukemia in MS patients and review the current literature data.

Case report

Case 1

In 2000, this 53 year-old female patient presented spastic paraparesis and sensory symptoms leading to a diagnosis of MS. After three spinal relapses, she was treated first by Avonex and then by Betaferon. However, she entered in a secondary progressive phase of the disease in 2002. She was then treated with mitoxantrone from January 2003 to June 2004, with a cumulative dose of 96 mg/m². Fourteen months after the last infusion, she developed an acute myeloblastic leukemia (AML), FAB subtype M3, showing a translocation t(15;17)(q22;q21) and a PML/RARA fusion gene. Therapy included all-trans retinoic acid combined with chemotherapy, in frame of the HOVON 52 trial. This patient was still alive and in complete hematological, cytogenetic and molecular response, ten months after the diagnosis of AML. She is the only patient with therapy-related leukemia from a cohort of 61 patients treated with Mitoxantrone between 1991 and 2004 in our Department (Cliniques Saint-Luc, Brussels).

Case 2

In 1996, this 42 year-old male patient presented a right hemihypoesthesia leading to a diagnosis of MS. After a remission of eighteen months, he presented ataxia and right hemiparesis. He was treated with Betaferon from July 1998 to August 2001. However, progression of the disease occurred and he suffered from a spastic tetraparesis. Mitoxantrone was given from February 2002 to May 2003, with a total cumulative dose of 84 mg/m². He was then treated with low dose of methotrexate (7.5 mg weekly) for nine months since September 2003, and with azathioprine (100 mg daily) since May 2004. EDSS worsened to 8.0. An acute myeloblastic leukemia, FAB subtype M2/4, displaying a t(8 ;21)(q22 ;q22) translocation and a AML1/ETO fusion gene was diagnosed in October 2005. The patient refused any treatment and died one month later.

Discussion

In addition to our two cases, we are aware of 29 other MS patients who developed leukemia after

Table I

Case	Authors	Gender, age (years)	Cumulative Dose (mg/m²)	Type of leukemia FAB classification	Onset after end of Mitoxantrone (months)	Cohort
1	Vicari, 1998	M, 36	50	M3; t (15;17)	60	
2	Brassat, 2002	F, 30	67	M5; t (9;11)	15	*
3	Radu, 2002	F, 24	70	Not specified	5	–
4	Cattaneo, 2003	M, 56	110	M3; t (15;17)	14	**
5	Heesen, 2003	F, 34	72	M4Eo; inv (16)	5	1/59
6	Goodkin, 2003	M, 48	110	M1; t (8;21)	3	–
7	Goodkin, 2003	F, 32	unknown	Not specified	unknown	–
8	Beaumont, 2003	F, 28	120	M3; t (15;17)	16	–
9	Tanasescu, 2004	M, 46	96	M1; t (8;21)	6	–
10	Voltz, 2004	F, 45	48	M4Eo : inv (16)	28	1/644
11	Novoselac, 2004	F, 43	60	M3; t (15;17)	11	–
12	Delisse, 2004	F, 49	80	M3; t (15;17)	26	1/255
13	Arruda, 2005	F, 47	12	M3; t (15;17)	30	–
14	Tellez, 2005	F, 26	72	Not specified	3	1/69
15	Nollet, 2006	F, 40	36	M3; t (15;17)	30	–
16	Nollet, 2006	F, 52	96	M4; t (9;11)	19	–
17	Ledda, 2006	F, 21	120	M3; t (15;17)	18	–
18	Ledda, 2006	F, 37	144	M3; t (15;17)	7	–
19	Lynn, 2006	M, 58	96	M3; t (15;17)	18	3/119
20	Lynn, 2006	M, 58	48	M3; t (15;17)	unknown	–
21	Ramtahal, 2006	M, 28	66	M3; t (15;17)	9	1/120
22	Cartwright, 2007	F, 40	120	ALL; t (11;19)	6	–
23	Cordioli, 2007	F, ?	60	M3; t (15;17)	unknown	**
24	Cordioli, 2007	F, ?	22.5	M3; t (15;17)	unknown	**
25	Cordioli, 2007	F, ?	130	M3; t (15;17)	unknown	** 4/170
26	Sadiq, 2008	F, 44	96	Chronic myeloid leukemia	18	–
27	Le Page, 2008	F, 37	70	M4	5	* 2/802
28	Ramkumar, 2008	F, 51	90	M3; t (15;17)	22	–
29	Ramkumar, 2008	F, 48	96	M3; t (15; 17)	2	–
30	Present case 1	F, 56	96	M3; t (15;17)	14	1/61
31	Present case 2	M, 54	84	M2/4; t (8;21)	28	–

FAB : French-American-British classification
M1 : myeloblastic leukemia without maturation
M3 : hypergranular promyelocytic leukemia (APL)
M4 : myelomonocytic leukemia
M4Eo : variant, increase in marrow eosinophils
M5 : monocytic leukemia
ALL : acute lymphoblastic leukemia
Translocation : t
Inversion : inv
*/** same cohorts of patients

mitoxantrone treatment (Table I). There were 23 females (79%) and age varied from 21 to 58 years (mean : 41.7). Seven out 28 (25%) were older than 50. The subtype of acute leukemia was not specified in three cases.

Eighteen (64%) out of the 28 well characterized cases developed acute promyelocytic leukemia (APL, also called M3 subtype). The total cumulative dose varied largely, between 12 and 144 mg/m² (mean : 80 mg/m²), indicating the absence of a dose-related effect. The interval between the end of the treatment and the leukemia varied between 7 and 60 months (mean : 20 months).

Five patients developed an acute myelomonocytic leukemia (M4 subtype, M2/4 and M4 Eosinophils), with different chromosomal translocations or inversions. The cumulative dose of these patients varied between 48 and 96 mg/m² (mean : 74 mg/m²). The interval between the end of the treatment and the leukemia varied between 5 and 28 months (mean : 17 months).

Two patients developed a myeloblastic leukemia without maturation (M1 subtype), 3 and 6 months after the end of the treatment (cases 6 and 7, Table I). One patient developed a monocytic leukemia (M5 subtype) 13 months after the end of the treatment (case 2).

Only one patient developed an acute lymphoblastic leukemia (ALL) 6 months after the end of the treatment with the translocation t(11;19)(q23;p13) involving the MLL gene (case 22 in the Table). Another patient developed a chronic myeloid leukemia (case 26).

Although t(15;17) genomic breakpoints are common sites of mitoxantrone-induced cleavage by topoisomerase II (Mistry *et al.*, 2005), the frequency of this chromosomal aberration was strikingly high (64%) in the MS population. By comparison, the same translocation was observed in only 1 out of 10 patients with breast cancer and mitoxantrone-related AML (Linassier *et al.*, 2000), and this type of translocation occurs in only 10 to 15 percent of

spontaneous cases of AML. The difference in frequency of APL (M3) between MS and breast cancer patients could be due to the simultaneous use of other anti-mitotic agents in the latter group (cyclophosphamide, fluorouracil, vindesine).

As the total number of MS patients treated with mitoxantrone is unknown, it is difficult to determine the accurate incidence rate of mitoxantrone-related leukemia in this population. An estimate of 0.07% has been reported on the basis of a review of three series comprising over 1300 patients (Ghalie *et al.*, 2002). However, this estimate could be an underestimation due to the failure of reporting cases, or lack of a strict follow up. In our literature review, 15 patients were described from cohorts totalizing 2299 patients, leading to an incidence rate of 0.65%.

Neurologists should be aware of this potentially severe adverse event. However, a mitoxantrone-related acute leukemia has a better prognosis than leukemia induced by alkylating agents, and a successful cure was obtained in most reported patients.

Acknowledgements

The authors are thankful to Dr. L. Michaux, hematologist, for helpful discussion.

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