

# ACUTE MYELOID LEUKAEMIA INDUCED BY MITOXANTRONE

## Case report

*Walter Oleschko Arruda<sup>1,2</sup>, María Belén Montú<sup>3</sup>,  
Marcelo de Souza R. de Oliveira<sup>4</sup>, Ricardo Ramina<sup>5</sup>*

**ABSTRACT** - Mitoxantrone (MX) is an immunosuppressant drug used in secondarily progressive multiple sclerosis (SPMS) and in relapsing-remitting multiple sclerosis (RRMS). It has a leukemogenesis potential induced by cytogenetic abnormalities, though with a low incidence. Promyelocytic leukaemia (type M3) and other forms of acute myeloblastic leukaemias (M4 and M5) have been described in a few MS patients who received MX during their treatment. We describe a white female patient, 47 year-old, with SPMS (EDSS = 4) with 14 years of disease. She received MX during her disease and developed acute promyelocytic leukaemia (M3), with severe thrombocytopenia 30 months later. She ultimately died due to intracerebral hemorrhage. Other cases of treatment related to AML are reviewed and discussed.

**KEY WORDS:** multiple sclerosis, mitoxantrone, acute myeloblastic leukemia.

### **Leucemia mielóide aguda induzida por mitoxantrone: relato de caso**

**RESUMO** - Mitoxantrone (MX) é uma agente imunossupressor utilizado nas formas progressivas secundárias de esclerose múltipla (EM) ou formas surto-remissão sem resposta com outras formas de tratamento (p.ex. beta-interferon, acetato de glatirâmer). Com o uso desta medicação, ocorre uma incidência maior, embora pequena, de desenvolvimento de leucemia mielóide aguda induzida por quimioterápicos. Descrevemos o caso de uma paciente com forma progressiva secundária de EM, submetida a uma dose única de MX de 15mg e que 30 meses após desenvolveu quadro fulminante de leucemia promieloblástica aguda (M3), com trombocitopenia grave. A paciente faleceu por hemorragia intracerebral maciça. É feita revisão de outros casos relatados na literatura e os possíveis mecanismos de desenvolvimento desta complicação grave secundária ao uso do MX.

**PALAVRAS-CHAVE:** esclerose múltipla, mitoxantrone, leucemia mielóide aguda.

Mitoxantrone (MX) is a DNA-topoisomerase II inhibitor widely used in cancer therapy. In addition, mitoxantrone induces immunodepletion. It is the first immunosuppressant approved for worsening relapsing and secondary progressive multiple sclerosis (MS)<sup>1,2</sup>. The incidence of acute myeloblastic leukemia (AML) in the population of MS patients treated with mitoxantrone is higher than the estimated incidence proportion of de novo AML in the global population<sup>3</sup>.

We report a case of fatal AML in a woman with MS who developed AML after use of MX. This is the first case of AML in a series of 25 patients with MS treated with MX in our Service.

### **CASE**

A 47-year-old woman had a diagnosis of definite MS picture for 14 years. During the first months of 2001 she entered the secondarily progressive phase with progressive right spastic hemiparesis, neurogenic bladder, and

Instituto de Neurologia de Curitiba, Curitiba PR, Brasil: <sup>1</sup>MD, Neurologist; <sup>2</sup>Assistant Professor, Universidade Federal do Paraná; <sup>3</sup>MD, Post-graduation in Neurology; <sup>4</sup>MD, Oncologist; <sup>5</sup>MD, PhD, Chairman.

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Dr. Walter Oleschko Arruda - Rua Jeremias Maciel Perretto 300 - 81210-310 Curitiba PR - Brasil. E-mail: arruda@inc-neuro.com.br

pyramidal signs. MX use was indicated and she received a first cycle on August, 2001 (12 mg/m<sup>2</sup>; total dose 15 mg). She developed a significant strength worsening of inferior right limb after administration and amenorrhea. She also refused to receive a further dose of MX. Intramuscular interferon beta-1a was started, despite of no clear indication based on the literature, but her clinical picture did not show any further clinical worsening (EDSS) since then for 28 months.

On February, 2004 she was hospitalized with a five days history of spontaneous diffuse hematomas all over her body surface, general status worsening, intermittent fever, and a hemorrhoidal thrombosis. At hospitalization, she was conscious, her examination disclosed a grade 4 (MRCP) right inferior limb paresis, intense asthenia, dizziness, urinary incontinence and painless cervical lymph nodes. Her EDSS was 4,0. Laboratory tests showed: 46,100 blood white cells, 97% blasts, with Auer rods (Faggot cells), thrombocytopenia (20,000/mm<sup>3</sup>), bleeding time 2.6 minutes, coagulation time 15 minutes, PTA (RNI = 2.56), KPTT 45 seconds (control 29.9 s), hemoglobin 8.3 g/dL, microcytosis, ESR 70 mm (first hour), creatinine 1.4 mg/dL (0.4-1.3), AST 37 UI/L (5-34), ALT 45 UI/L (10-35), reactive C protein = 768 mg/L (normal < 6.0), and  $\alpha$ 1-glycoprotein = 387,9 mg/dL (40-120). Immunophenotyping showed 20% of cells with significant expression for CD2, CD45, CD13, CD34 and CD117. HLA-DR was negative. These findings were in keeping with LMA-M3. She received 3 platelets units and vitamin K.

Forty-eight hours after admission she developed acute respiratory failure, became torporous, started vomiting, and anisocoria with right-sided mydriasis was observed. A CT-scan disclosed an extensive acute right subdural hematoma, and a right temporal intraparenchymal hemorrhage with midline deviation. A decompressive craniotomy and surgical drainage was performed, after receiving hemoderivates. Shortly after the surgical drainage of the intracerebral hematomas, she developed refractory arterial hypotension and shock, and died a few hours later.

## DISCUSSION

There are two forms of therapy-related AML (trAML) on the basis of the type of chemotherapy used. The first form is classically induced by alkylating agents (cyclophosphamide, nitrosureas), five to seven years after starting treatment. The second form of trAML appears in 2% to 12% of cases after the use of topoisomerase II inhibitors like MX from two to four years after starting treatment<sup>4,5</sup>. trAML following DNA-topoisomerase II inhibitors, such as

anthracyclines, epipodophyllotoxins, or MX, has a short latency period (2 years), an acute onset, and is associated with cytogenetic abnormalities similar to that of de novo acute leukemia, such as t(8;21), t(15;17), or balanced translocations involving 11q23 band. MLL gene rearrangement in 11q23 is frequently involved in both AML and acute lymphoblastic leukemia, which is developed in patients treated with DNA-topoisomerase II inhibitors. Drug-induced DNA breaks on MLL gene-specific sites result in fusion products that are believed to play a critical role in leukemogenesis<sup>6</sup>. Unfortunately, cytogenetic studies were not performed in our patient.

Ghalie et al.<sup>7</sup> evaluated the incidence of therapy related acute leukemia after MX reviewing the records of 1,378 MX recipients in three MS studies (mean cumulative dose of 60 mg/m<sup>2</sup> and mean follow-up of 36 months) and found only one case of acute promyelocytic leukaemia (APML) detected five years after initiating MX (mean incidence proportion 0.07%). Brassat et al.<sup>6</sup> detected only one case of trAML (FAB M5) (in a cohort of 802 French patients with MS treated with MX (incidence  $\cong$  0.25%). Cattaneo et al.<sup>8</sup> described another case of promyelocytic leukaemia (FAB M3) in a 56-year-old man, which appeared 14 months after receiving a cumulative dose of 198 mg of MX.

In fact, promyelocytic leukaemia (FAB M3), together with M4 and M5, is among the typical FAB subtypes of AML/myelodysplasia induced by topo-II inhibitors. Moreover, the incidence of trAML in MX treated MS patients is higher than the estimated incidence of de novo AML, which ranges between 0.001% to 0.03%, according to the age (apud Gallie et al.<sup>8</sup>).

Our patient received a single dose of 15 mg of MX, when it was stopped due to amenorrhea and clinical worsening. She also refused to keep using this form of treatment. Nevertheless, the risk related to cumulative dosage has not been clearly established yet.

In addition, the role of beta-interferon as contributory factor for leukemogenesis cannot be excluded, though there are neither patient series data nor reports to support this hypothesis. This possibility is unlikely to be true due to the great number of MS patients under use of beta-interferons and no report of such association up to now. Although a de novo leukemia cannot be completely excluded in our case,

the pathogenetic link between the use of MX and the development of trAML seems to be supported by the previous reports of these cases in the literature.

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## REFERENCES

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. *N Engl J Med* 2000;343:938-952.
2. 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.
3. 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.
4. Pedersen-Bjergaard J, Philip P. Two different classes of therapy related and de novo acute myeloid leukemia? *Cancer Genet Cytogenet* 1991;55:119-124.
5. Pedersen-Bjergaard J, Philip P, Larsen SO, Jensen G, Byrting K. Chromosome aberrations and prognostic factors in therapy-related myelodysplasia and acute nonlymphocytic leukemia. *Blood* 1990;76:1083-1091.
6. Brassat D, Recher C, Waubant E, et al. Therapy-related acute myeloblastic leukemia after mitoxantrone treatment in a patient with MS. *Neurology* 2002;59:954-955.
7. 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.
8. 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.