

# Acute Promyelocytic Leukemia Associated with Therapy of Mitoxantrone in Multiple Sclerosis

Multipl Sklerozisde Mitoksantron Tedavisiyle İlişkili Akut Promyelositik Lösemi  
Hematoloji

Başvuru: 17.09.2015  
Kabul: 08.02.2016  
Yayın: 08.02.2016

Gülden Sincan<sup>1</sup>, Yusuf Bilen<sup>1</sup>, Fuat Erdem<sup>1</sup>, Suat Sincan<sup>1</sup>

<sup>1</sup> Atatürk Üniversitesi Tıp Fakültesi

## Özet

Mitoksantron, relaps ve progresif multiple sklerozis tedavisinde kullanılan bir DNA- topoizomaz inhibitörüdür. Mitoksantron kullanımı, mitoksantronun kardiyotoksik ve tedavi-ilişkili akut lösemi potansiyel riskleri nedeniyle kısıtlıdır. Translokasyon (15,17) pozitif akut promyelositik lösemi mitoksantron kullanan kanser hastalarıyla karşılaştırıldığında multipl sklerozisli hastalarda daha sık görülür. Bu komplikasyonun zamanı, riski, mortalitesi ve maruziyetle ilişkisi belirsizdir. Bu nedenle, mitoksantron son dozundan sonraki 5 yıl boyunca hematolojik monitorizasyon devam etmelidir. Bu çalışmada, biz 20 yıldır multipl sklerozis hastası olan bir olguu sunuyoruz. Bu hastada mitoksantron tedavisinin son dozundan 17 ay sonra pansitopeni gelişti. Biz laboratuvar bulgularıyla akut promyelositik lösemi saptadık. Bu hastaya remisyon indüksiyon ve all-trans retinoik asit tedavisi başladık. Hasta pulmoner aspergillozis nedeniyle öldü.

**Anahtar kelimeler:** Akut promyelositik lösemi, Mitoksantron, Multipl sklerozis

## Abstract

Mitoxantrone is a DNA-topoisomerase 2 inhibitor used for treatment of relapsing and progressive multiple sclerosis. Usage of mitoxantrone is limited, because of its potential risk such as cardiotoxicity and the induction of therapy-related acute leukemia. Acute promyelocytic leukemia with the translocation t(15;17) was over-represented in the multiple sclerosis population in comparison with cancer patients also treated with mitoxantrone. The timing of this complication, risk, mortality and relationship to exposure remain uncertain. Therefore, haematological monitoring should continue for at least 5 years after the last dose of mitoxantrone. In these report; we present a case with multiple sclerosis for 20 years. Pansitopenia developed in these patient after 17 months after receive the last dose of mitoxantrone (Cumulative dose:120 mg). We determined acute promyelocytic leukemia with laboratory finding. Remission induction chemotherapy and all-trans retinoic acid was administered to these patient. She was died because of pulmonary aspergillozis.

**Keywords:** Acute promyelocytic leukemia, Mitoxantrone, Multiple sclerosis

## Introduction

Multiple sclerosis (MS) is a chronic autoimmune demyelinating disease affecting central nervous system. Mitoxantrone was the first immunosuppressive agent for treatment of relapsing and progressive MS. In recent years, its use has decreased due to the risk of severe adverse events such as cardiotoxicity and induction of treatment related acute promyelocytic leukemia (t-APL). 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>1</sup> Treatment related acute myeloblastic leukemia (t-AML) appears in 2% to 12% of cases after the use of topoisomerase II inhibitors such as mitoxantrone from two to four years after starting treatment.<sup>2-3</sup> T-APL typically occurs without an antecedent myelodysplastic phase.<sup>4</sup> We present the patient with multiple sclerosis and t-APL because of rarity in this paper.

## Case Report

A 42 years old female patient was admitted to in neurology clinic inability to walk and general status worsening. Her past medical history included of multiple sclerosis for 20 years. Patient received interferon beta-1a initially. Then she received eight cycles of mitoxantrone (10 mg/ m<sup>2</sup>; cumulative dose:120 mg) , due to lack of response to interferon. It passed 17 months, after the last dose of mitoxantrone. After fingolimod and prolonged-release fampridine was started to the patient due to inadequate response to treatment with mitoxantrone. On evaluation of her routine laboratory tests, she was found to have haemoglobin of 11 g/dl, haematocrit of 32.3%, white blood cell count of 1.600/mm<sup>3</sup>, neutrophil count of 700/ mm<sup>3</sup> and platelet count of 19000 µl. Level of serum urea was 27 mg/dl, creatinine 0.6 mg/dl, sodium 137 mEq/L, potassium 3.7 mEq/L, uric acid 7.7 mg/dl, total protein 6.7 mg/dl, albumin 4.1 mg/dl, aspartate aminotransferase 26 UI/L, alanine aminotransferase 22 UI/L, gamma glutamyl transferase 39 U/L, lactate dehydrogenase 395 UI/L. Prothrombin time and activated partial thromboplastin time were within the reference range. The patient was consulted to our clinic because of pancytopenia. A large number of blasts (90%) with abundant cytoplasmic granules detected in peripheral blood smear (Image 1 and 2). The patient was transferred to our clinic. Bone marrow aspirate demonstrated a markedly hypercellular marrow with 20% blast cells and 80% abnormal promyelocytes.

Flow cytometry study demonstrated these cells to be phenotypically positive for CD13, CD33, myeloperoxidase (MPO), and negative for HLA-DR. PML/RAR-alpha fusion gene rearrangement was confirmed by fluorescence in situ hybridization and molecular analysis. The patient was diagnosed as having t-APL, and remission induction chemotherapy with doxorubicin (45 mg/m<sup>2</sup> for 3 days), cytarabine (200 mg/ m<sup>2</sup> for 7 days) and all-trans retinoic acid (45 mg/m<sup>2</sup> ) was administered. A bone marrow study performed on day +28 showed complete morphologic, cytogenetic and molecular remission. Consolidation therapy could not be given to patients because of fungal pneumonia. She died after 40 days of remission induction therapy, because of pulmonary aspergillosis.

## Case Discussion

Mitoxantrone hydrochloride is an anthracenedione developed as an antineoplastic agent. It reduces lymphocyte proliferation with several mechanisms such as inhibition of the DNA repair enzyme topoisomerase II. The United States Food and Drug Administration (FDA) extended approval for the treatment of aggressive, relapsing, and progressive-relapsing multiple sclerosis in 2000.<sup>5</sup> Mitoxantrone therapy is associated with systolic dysfunction and therapy-related acute leukemia. Systolic dysfunction occurs in 12% of patients with MS treated with mitoxantrone, congestive heart failure occurs in 0.4%, and leukemia occurs in 0.8%.<sup>6</sup>

The cumulative exposure to chemotherapy with alkylating agents and topoisomerase II inhibitors is associated with t-AML that may develop any time after the completion of the treatment.<sup>7</sup> T-AML following DNA-topoisomerase II inhibitors, such as anthracyclines, epipodophyllotoxins, or mitoxantrone is associated with cytogenetic abnormalities such as t(8;21), t(15;17), or balanced translocations involving 11q23 band.<sup>8</sup>

The incidence of t-AML in mitoxantrone treated MS patients is higher than the estimated incidence of de novo AML. The first case report of t-AML in a patient with MS was published in 1998.<sup>9</sup> Cattaneo et al. described a case of promyelocytic leukaemia in a 56-year-old man, which appeared 14 months after receiving a cumulative dose of 198 mg of mitoxantrone.<sup>10</sup> Ghalie et al. evaluated the incidence of therapy related acute leukemia after mitoxantrone reviewing the records of 1,378 mitoxantrone 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 t-AML detected five years after initiating mitoxantrone (mean incidence proportion 0.07%).<sup>11</sup>

In our patient, APL developed after 17 months from the end of a full-dose course of mitoxantrone. No myelodysplastic phase was documented before its onset. The patient had received neither other types of cytostatic drugs nor radiotherapy. The contributory role of  $\beta$ -interferon cannot be excluded, but no reports exist to date on the leukaemogenic activity of  $\beta$ -interferon.

Conclusion; acute promyelocytic leukemia with the translocation t(15;17) was over-represented in the MS population in comparison with cancer patients also treated with mitoxantrone. The timing of this complication, risk, mortality and relationship to exposure remain uncertain. Haematological monitoring should continue for at least 5 years after the last dose of mitoxantrone.<sup>12</sup>

## References

1. Tanasescu R, et al. Acute myeloid leukaemia induced by mitoxantrone in a multiple sclerosis patient. *J Neurol.* 2004;251:762-763.
2. Pedersen-Bjergaard J, Philip P. Two different classes of therapy related and de novo acute myeloid leukemia?. *Cancer Genet Cytogenet.* 1991;55:119-124.
3. Pedersen-Bjergaard J, et al. Chromosome aberrations and prognostic factors in therapy-related myelodysplasia and acute nonlymphocytic leukemia. *Blood.* 1990;76:1083-1091.
4. Ammatuna E, Montesinos P, Hasan SK et al. Presenting features and treatment outcome of acute promyelocytic leukemia arising after multiple sclerosis. *Haematologica.* 2011; 96(4): 621–625
5. Fox EJ. Mechanism of action of mitoxantrone. *Neurology.* 2004 (28);63:15-18.
6. Marriott JJ, et al. Evidence Report: The efficacy and safety of mitoxantrone (Novantrone) in the treatment of multiple sclerosis: Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2010;74(18):1463-1470.
7. Rashidi A, Fisher SI. Therapy-related acute promyelocytic leukemia: a systematic review. *Med Oncol.* 2013; 30(3): 625.
8. Brunning RD, et al. Acute myeloid leukaemias and myelodysplastic syndromes, therapy related. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, editors. *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues.* IARC press: Lyon; 2001. p. 89–91.
9. Vicari AM, et al. Acute promyelocytic leukemia following mitoxantrone as single agent for the treatment of multiple sclerosis. *Leukemia.* 1998; 12: 441–442.
10. Cattaneo C, et al. A case of acute promyelocytic leukaemia following mitoxantrone treatment of multiple sclerosis. *Leukemia.* 2003;17:985-986.
11. Ghalie RG, et al. A study of therapy-related acute leukaemia after mitoxantrone therapy for multiple sclerosis. *Mult Scler.* 2002;8:441-445.
12. Pascual AM, et al. Revision of the risk of secondary leukaemia after mitoxantrone in multiple sclerosis populations is required. *Mult Scler.* 2009 Nov;15(11): 1303-1310.