

Therapy-related myelodysplastic syndrome following acute promyelocytic leukemia and biphenotypic acute leukemia following stem cell transplantation in the same patient

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Received: Sep 09, 2006 • Accepted: Mar 26, 2007

ABSTRACT

Therapy-related myelodysplastic syndrome in patients with acute promyelocytic leukemia is a rare event and the prognosis is poor. Allogeneic bone marrow transplantation is recently being reported as an effective treatment. We present a young patient with acute promyelocytic leukemia who developed myelodysplastic syndrome 52 months after complete remission. She underwent allogeneic peripheral blood stem cell transplantation but relapsed with biphenotypic leukemia after five months. To our knowledge, this is the first case to relapse with acute biphenotypic leukemia after allogeneic peripheral stem cell transplantation for therapy-related myelodysplastic syndrome following acute promyelocytic leukemia.

Key Words: Acute promyelocytic leukemia, therapy-related myelodysplastic syndrome, allogeneic peripheral blood stem cell transplantation, prognosis, biphenotypic leukemia

ÖZET

Aynı hastada gelişen akut promiyelositik lösemi sonrası miyelodisplastik sendrom ve kök hücre nakli sonrası bifenotipik lösemi

Akut promiyelositik lösemili hastalarda tedaviye bağlı miyelodisplastik sendrom nadir bir olaydır ve prognozu kötüdür. Son dönemde allogeneik kök hücre naklinin etkili bir tedavi şekli olduğu bildirilmektedir. Biz de tam remisyondan 52 ay sonra miyelodisplastik sendrom gelişen akut promiyelositik lösemili genç bir hastayı sunduk. Hastaya allogeneik kök hücre nakli yapıldı ancak 5 ay sonra bifenotipik lösemi gözlemlendi. Bildiğimiz kadarıyla bu olgu tedaviye bağlı miyelodisplastik sendrom nedeniyle yapılan allogeneik periferik kök hücre nakli sonrası bifenotipik lösemi şeklinde relaps gelişen ilk olgudur.

Anahtar Sözcükler: Akut promiyelositik lösemi, tedaviye bağlı miyelodisplastik sendrom, allogeneik periferik kök hücre nakli, prognoz, bifenotipik lösemi

INTRODUCTION

The occurrence of therapy-related myelodysplastic syndrome (t-MDS) and therapy-related acute myelogenous leukemia (t-AML) after treatment for other malignant disorders is one of the late effects of treatment. Among chemotherapy agents, alkylating drugs and topoisomerase II inhibitors have been frequently associated with development of t-MDS/AML^[1]. The incidence of t-MDS/AML after acute promyelocytic leukemia (APL) ranges from 1% to 6.5%^[2]. In the literature, less than 50 cases of t-MDS/AML after APL are reported.

CASE REPORT

A 32-year-old female patient was presented in March 2000 with fatigue, fever and bruising. Her hemoglobin level was 5.3 g/dl, peripheral white blood count was $6.3 \times 10^3/\mu\text{l}$ and the platelet count was $13 \times 10^3/\mu\text{l}$. Disseminated intravascular coagulation was also diagnosed. The diagnosis of APL was made according to the French-American-British cooperative group classification criteria. Cytogenetic and fluorescence in situ hybridization (FISH) analysis showed the classical translocation t(15;17). The patient received idarubicin $12 \text{ mg}/\text{m}^2/\text{day}$ intravenously (I.V.) for 4 days as induction chemotherapy. She was also treated with all-trans retinoic acid (ATRA) $45 \text{ mg}/\text{m}^2/\text{day}$, but ATRA was discontinued because of rash and fever. She received idarubicin $5 \text{ mg}/\text{m}^2/\text{day}$ I.V. for 4 days and cytosine arabinoside (Ara-C) $1 \text{ g}/\text{m}^2/\text{day}$ I.V. for 4 days as first; mitoxantrone $10 \text{ mg}/\text{m}^2/\text{day}$ I.V. and etoposide $100 \text{ mg}/\text{m}^2/\text{day}$ I.V. (both for 5 days) as second; and idarubicin $12 \text{ mg}/\text{m}^2/\text{day}$ I.V. for 1 day, 6-thioguanine $70 \text{ mg}/\text{m}^2/\text{day}$ per os (P.O.) for 5 days and Ara-C $150 \text{ mg}/\text{m}^2/\text{day}$ subcutaneously (S.C.) for 5 days as third consolidation chemotherapy. In March 2001, maintenance chemotherapy with methotrexate $15 \text{ mg}/\text{m}^2/\text{week}$ intramuscularly (I.M.) plus 6-mercaptopurine $90 \text{ mg}/\text{m}^2/\text{day}$ P.O. was started and continued for two years.

In March 2004, progressive pancytopenia developed and the bone marrow examination was compatible with MDS with a 7% excess of blasts and dyserythropoietic changes (internuclear chromatin bridging and lobulated nuclei). Real time polymerase chain reaction (PCR) of the myelodysplastic marrow specimen was negative for t(15;17). The karyotype and FISH analysis revealed deletion of long arm chromosome 2 and del 7(q31). In December 2004, the patient underwent allogeneic peripheral blood stem cell

transplantation (PBSCT) from her HLA-compatible (6/6) mother. She received busulphan $0.8 \text{ mg}/\text{kg}$ q.i.d. I.V. on days -7,-6,-5,-4 and cyclophosphamide $60 \text{ mg}/\text{kg}/\text{day}$ I.V. on days -3, -2 as a conditioning regimen. The given CD 34 positive stem cell count was 6.83×10^6 per kilogram. $1.5 \text{ mg}/\text{kg}$ cyclosporine b.i.d. I.V. beginning from day -1 and methotrexate $15 \text{ mg}/\text{m}^2/\text{day}$ on day +1, $10 \text{ mg}/\text{m}^2/\text{day}$ on days +3, +6, +11 were given for graft versus host disease prophylaxis. Five months after PBSCT she relapsed with biphenotypic leukemia. Enough bone marrow material for a new cytogenetic examination could not be obtained but flow cytometry analysis revealed CD 79a, CD 10, CD 22, TdT, CD 13 and myeloperoxidase positivity. She did not respond to donor lymphocytes infusion and died in September 2005 because of sepsis.

DISCUSSION

We described a patient with APL treated without alkylating agents and acquired t-MDS with chromosome 2 and 7 abnormalities. Two different categories of t-MDS/AML have been observed to emerge^[3]. The first category is related to the exposure to alkylating agents used in chemotherapy. The disease usually has a latent period of 2-8 years before development of t-MDS/AML and is preceded by a MDS phase. Cytogenetically, it is characterized by -5/5q- and -7/7q- and responds poorly to chemotherapy. The second category usually develops as AML after exposure to cytostatic drugs such as epipodophyllotoxins and anthracyclines. This type of leukemia appears without an initial MDS phase, often 1.5-2.5 years after exposure^[4].

Our patient developed MDS 52 months after treatment of APL. Although she had never been treated with alkylating agents, the latency period and cytogenetic changes were like the alkylating agent-related MDS. The explanation of these findings remains unclear. It has been hypothesized that methotrexate and 6-mercaptopurine might modify the leukemogenic effect of anthracyclines^[1]. These observations also suggest that the associations proposed by WHO are not absolute and overlap may occur. Chromosome abnormalities usually observed after alkylating agents may also occur after anthracycline therapy^[1,5,6]. Some authors have suggested that genetic predisposition contributes to the onset of t-MDS^[7].

In several previous reports, the risk of t-MDS and t-AML after chemotherapy increased with

the patient's age. The median age was 48 (29-57) years^[6]. Increased duration of chemotherapy and number of relapses are also risk factors^[7]. Among chemotherapies, use of alkylating agents has been shown to be a significant risk factor for t-MDS and t-AML. There is no argument that ATRA provokes t-MDS or t-AML. Low-dose methotrexate and 6-mercaptopurine used during maintenance therapy of APL have been reported to be safe. Nevertheless, these drugs may enhance the risk of developing t-MDS or t-AML when used after other chemotherapies^[8]. Anthracyclines and etoposide (VP 16) are also known as leukemogenic drugs^[9]. Our patient was younger than 40 and had no relapses, so she seems to have had no risk except chemotherapy.

The prognosis of patients with t-MDS or t-AML is usually poor. The median survival is 10

(7-22) months. This poor survival is correlated with poor response to therapy. In young patients, allogeneic bone marrow transplantation has been recently reported as being effective^[10]. However, our patient relapsed and died despite having undergone allogeneic PBSCT.

In conclusion, this is a new case of MDS with chromosome 2 and 7 deletion after treatment for APL. We preferred allogeneic PBSCT as a treatment choice, but the prognosis remained poor. Chromosomal abnormalities usually observed after alkylating agents may also occur after anthracyclines, epipodophyllotoxins, methotrexate, and 6-MP therapy. Careful follow-up of APL survivors is also mandatory for the early diagnosis of t-MDS/AML. Since mortality of transplantation is not negligible, avoiding unnecessary toxicity can be much more important.

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