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Extramedullary relapse following allogeneic stem cell transplatation in acute promyelocytic leukemia: the role of ATRA

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Abstract

Extramedullary disease is rare in the course of acute promyelocytic leukemia (APL). It has been suggested that the administration of all-trans retinoic acid (ATRA) might increase this complication. Therefore, the administration of ATRA for the treatment of extramedullary relapse, in particular, after transplantation remains controversial. In our patient, a 42-year-old woman with APL, ATRA was effective in the treatment of extramedullary relapse with molecular evidence of disease in the bone marrow following allogeneic peripheral blood stem cell transplantation (AlloSCT). The patient has been leukemia-free and well for 32 months after ATRA administration. ATRA may be effective in patients with APL when extramedullary relapse occurs following AlloSCT. Acute promyelocytic leukemia (APL) is characterized by a specific balanced t(15;17) (q22;q21) chromosomal translocation. All-trans retinoic acid (ATRA) leads to the differentiation and/or apoptosis of APL cells and thus is a standard agent in the remission induction treatment of newly diagnosed AP.[1] However, the role of ATRA in the treatment of extramedullary disease, chloroma, a rare complication of APL,[2-15] is not clear yet. Furthermore, there is a concern about whether ATRA administration may increase extramedullary relapse.[2-6] Here we present a patient who developed extramedullary relapse in the middle ear with molecular evidence of disease in the bone marrow following allogeneic peripheral blood stem cell transplantation (AlloSCT). The patient was treated successfully with ATRA and local radiotherapy. Reverse Transcribed Polymerase Chain Reaction (RT-PCR) Analysis: DNA and RNA were isolated from peripheral blood and bone marrow biopsy samples according to standard protocols.[16] Analysis of the t(15;17) (q22;q21) translocation was achieved by detection of the fusion transcript of the PML and RARa genes by RT-PCR of the RNA molecule. A detailed description of the methods has been previously reported.[17] Briefly, following cDNA synthesis first round of RT-PCR was performed which yields a 435 bp amplicon. Subsequently, a second round of PCR was done with a second set of primers which amplify a 326 bp fragment in the presence of a fusion transcript which was interpreted as positivity for this translocation.

A 42-year-old woman was diagnosed as having APL in another university hospital in 1994. Mitoxantrone 12 mg/m^2/d i.v. for two consecutive days and cytarabine 100 mg/m^2/day i.v. for five consecutive days was administered as remission induction therapy. A combination of 6-thioguanine and cytarabine was administered for consolidation for two courses. The patient relapsed 6 months later and achieved a second complete (CR) remission with cytarabine and idarubucin. The patient was consolidated with the same regimen and then with high dose cytarabine. In March 1997, the patient underwent alloPBSCT from a HLA full-match sibling. The numbers of infused CD34+ cells and mononuclear cells were 4.5x10^6/kg and 3.4x10^8/kg, respectively. Cyclosporine (Cy) and short term methotrexate

were administered for graft versus host disease (GVHD) prophylaxis. Complete chimerism was shown by variable tandem repeat (VNTR) polymorphism at the +4th month. The patient did not develop acute GVHD. When Cy was being tapered, chronic limited GVHD occurred at the +8th month. Cy was discontinued at the +12th month. The patient presented with tinnitus, ataxia, and hearing loss a month later. A CT scan of the cranium and the cervical region showed a tumor in the left middle ear. A mass appeared in the left preacuricular area over 10 days. A fine needle aspiration of the tumor revealed chloroma. Her complete blood count (CBC) and the morphologic examination of the peripheral blood smear and the bone marrow aspirate were consistent with hematologic CR. The patient was treated with local radiotherapy. All symptoms of the ear involvement were resolved, and preauricular tumor disappeared. A repeated CT scan showed a significant decrease in diameter of the tumor in middle ear. When she came to the clinic for her follow-up visit one month after completing radiotherapy, pertinent feature of her physical exam was a mass in the left preauricular area. Chloroma was documented by a fine needle aspiration of the tumor. Her CBC and the morphologic examination of the peripheral blood and the bone marrow aspirate/biopsy were consistent with hematologic CR. A reverse transcribed polymerase chain reaction (RT-PCR) and fluorescence in situ hybridization (FISH) analysis of the bone marrow revealed PML-RARa positivity. Local radiotherapy was administrated to the left preauricular area, and ATRA was initiated at a dose of 45 mg/m2/day. Three months after ATRA administration, a pathologic examination of the bone marrow aspiration/biopsy revealed that her hematologic CR was still present. The RT-PCR analysis of the bone marrow aspirate became negative for PML-RARa. Six months after hematologic CR was documented, ATRA was discontinued. Three months after discontinuing ATRA, the RT-PCR analysis of the bone marrow aspirate revealed that PML-RARa negativity persisted. The patient has been complete hematologic and molecular remission for 32 months after ATRA administration. The skin and central nervous system (CNS) are the most common sites involved by extramedullary infiltration of APL.[2,5-8] The ear involvement has been reported in only 7 patients as occurred in our patient.[4,8,10-12] In APL patients, the treatment of chloroma is not well-determined since neither a study with large number patients nor a consensus on using ATRA is present. It has been suggested that ATRA administration may increase extramedullary relapse[2-6] by modulating the expression of adhesion molecules in endothelial and leukemic cells, such as CD56, CD18, CD13 and Lfa-1, VCAM-1, VLA4, ICAM-1.[2-6] In contrast, ATRA was used successfully to treat extramedullary relapse in some patients,[4,9.10] two of whom received ATRA before relapse.[4,10] Our patient did not receive ATRA before extramedullary relapse. Her chloroma was detected after AlloSCT and was associated with molecular evidence of disease in the bone marrow. There have been a few cases with APL who developed chloroma after allogeneic hematopoietic stem cell transplantation.[13-15] These patients were treated with different chemotherapy regimens without ATRA or donor leukocyte infusions because ATRA was thought to be the possible cause of extramedullary relapse. In our patient, local radiotherapy did not prevent recurrence of chloroma. After addition of ATRA to local radiotherapy, chloroma did not recur, and PML-RARa became negative. Furthermore, the patient remains in complete hematologic and molecular remission at 32 months. Considering the fact that systemic relapse may often follow PML-RARa positivity or extramedullary relapse in patients with APL.[1,11,18] we assume that ATRA not only prevented recurrence of chloroma, but also prevented systemic relapse after stem cell transplantation in our patient. Compared to other therapeutic options such as chemotherapy, high dose chemotherapy with autologous transplantation, or second allogeneic transplantation, ATRA administration may be considered as a safe and effective approach in these patients. However, a study of a large series of patients is warranted to establish the definitive role of ATRA in the treatment of extramedullary relapse of APL.

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