Recurrent Relapses of Acute Myelogenous Leukemia in the Isolated Extramedullary Sites Following Allogeneic Bone Marrow Transplantations

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Abstract

Isolated extramedullary (EM) relapses of acute myelogenous leukemia (AML) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) have been reported to be rare, and are usually followed by bone marrow relapses. We report a 49-year-old man with AML with the unfavorable chromosome abnormality 7q-, who was treated by allo-HSCT. Fifteen months after allo-HSCT, the patient initially developed a relapse only in his inguinal lymph nodes, and then bone marrow relapse became evident one month after the EM relapse. Subsequently, the patient received chemotherapy and a second allo-HSCT from another donor, but he suffered another relapse in different EM sites including the skin and central nervous system with a persistently normal marrow. This case is characterized by repeated relapses in isolated EM sites after allo-HSCT and suggests that the anti-leukemic effects of chemotherapy and/or graft-versus-leukemia effects in the EM sites might not be so uniformly effective as that in the marrow. Accordingly, we should be aware that AML relapses can occur repeatedly only in isolated EM sites post allo-HSCT, resulting in treatment failure and a poor prognosis.

Key words: extramedullary, relapse, AML, allo-BMT, GVL

Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is a potentially curative therapy for patients with acute myelogenous leukemia (AML) based upon graft-versus-leukemia (GVL) effects in addition to the intensive conditioning chemo-radiotherapy. However, some patients eventually develop a relapse following allo-HSCT, resulting in treatment failure and a poor prognosis. AML relapse usually occurs in the bone marrow, but a small fraction of patients develop extramedullary (EM) relapses either alone or concomitant with bone marrow relapse (1-5). Bekassy et al reported isolated EM relapse occurred after allo-BMT in 20 out of 3,071 AML patients (0.65%) (1). Little is known concerning the mechanism of EM relapse; however, the prognosis of patients with an EM relapse of AML is generally considered to be less favorable than that of AML patients with bone marrow relapse only (1, 6, 7).

We present a case of AML who developed a relapse confined to his inguinal lymph nodes 15 months after allogeneic bone marrow transplantation (allo-BMT). Following a second allo-BMT from another donor, the patient had multiple relapses in different EM sites such as the skin and central nervous system, with a persistently normal marrow. Frequent relapses in EM sites suggest that the GVL effect in the EM sites was not as potent as that in the bone marrow, where it remained effective. Thus, we should note that AML relapses can occur in isolated EM sites because the GVL effect might not be uniformly effective throughout the body following allo-HSCT.

Case Presentation

In June 2002, a 49-year-old Japanese man was referred to us for evaluation of leukocytosis and anemia. At the time of
hospitalization, hemoglobin was 7.4 g/dl; platelet count, 135×10^9/l; white blood cell count, 32.3×10^9/l with 2% neutrophils, 9% lymphocytes, and 89% myeloblasts that stained positive for myeloperoxidase (MPO). A bone marrow aspirate was hypercellular with 91% myeloblasts, which were positive for CD7, CD13, CD15, CD33, CD34 and HLA-DR. Cytogenetic analysis of the bone marrow cells revealed 46 XY, 7q- in all metaphase cells. A diagnosis of AML-M1 type was made according to the French-American-British classification, and this patient with the 7q- chromosome abnormality was categorized as having a poor prognosis with an approximately 75% chance of relapse (8, 9). Extramedullary leukemia was not documented at diagnosis. The patient was treated with a conventional induction regimen consisting of idarubicin and cytarabine (CA), and he achieved a complete remission (CR). He was treated with two further cycles of consolidation chemotherapy consisting of intermediate-dose CA combined with mitoxantrone in the first course and etoposide in the second course, as described previously (10). During the consolidation chemotherapy, the patient developed invasive pulmonary aspergillosis, which was treated by administration of Amphotericin-B. Finally, local lung resection of left upper lobe was performed prior to allo-BMT.

In February 2003, the patient underwent an allo-BMT from an HLA matched unrelated donor after receiving busulfan (16 mg/kg) and cyclophosphamide (120 mg/kg). Graft-versus-host disease (GVHD) prophylaxis consisted of cyclosporine (CyA) and a short course of methotrexate (MTX). During the neutropenic period, the patient developed pulmonary abscess caused by Streptococcus pneumoniae, however, it gradually stabilized in response to antibiotic therapy. Engraftment was obtained on day 17, and a bone marrow examination demonstrated continuing CR. A chimeric analysis of the minisatellite variable number of tandem repeats disclosed that his bone marrow cells consisted entirely of donor-derived cells. On day 38, the patient developed grade I acute GVHD confined to his skin, which disappeared without any treatment. Four months after allo-BMT, the patient disclosed typical oral manifestations of chronic GVHD, which were resolved after adjusting the dose of CyA.

In May 2004, 15 months after BMT, the patient developed bilateral inguinal lymphadenopathy. He was otherwise asymptomatic with no organomegaly and a normal complete blood count. A biopsy of a left inguinal lymph node revealed the infiltration of medium-sized blastic cells with moderately irregular nuclei (Fig. 1). These cells were positive for CD7, CD13, CD33, CD34 and HLA-DR, the same phenotype as that seen in his bone marrow at presentation. Chimeric analysis demonstrated that the lymph node cells were recipient derived, and a deletion of 7q was documented by cytogenetic analysis. In contrast, a bone marrow aspirate showed no infiltration by AML cells and also a donor-derived pattern by chimeric analysis. Further systemic investigation including computed tomography of the whole body and lumbar puncture of his cerebrospinal fluid showed no leukemic involvement of his other organs except for the inguinal lymph nodes. Based on these observations, isolated EM relapse of AML confined to the lymph nodes was diagnosed. Another donor search was initiated immediately for a second allo-SCT. The immunosuppressant was discontinued to induce a GVL effect; however, no improvement in his lymphadenopathy was seen. One month after the discontinuation of immunosuppression, a bone marrow aspirate showed an increase in the number of AML blasts, which accounted for up to 11% of the bone marrow nucleated cells. Cytogenetic analysis also demonstrated the emergence of cells with a deletion of 7q, and 15% of his bone marrow cells were recipient-derived by chimeric analysis. Thus, the patient suffered a relapse of AML in his bone marrow following an isolated EM relapse in his lymph nodes. Re-induction chemotherapy consisting of daunorubicin and CA was administered. The inguinal lymphadenopathy disappeared soon after chemotherapy; however, the number of AML blasts still increased peripherally and in his marrow. Another two courses of chemotherapy, using the CAG-regimen (11), were ineffective in inducing a CR.

In November 2004, the patient underwent a second allo-BMT from another HLA matched unrelated donor after receiving a reduced intensified conditioning (RIC) regimen consisting of fludarabine (180 mg/m²), busulfan (8 mg/kg), and total body irradiation (2 Gy). Acute GVHD prophylaxis consisted of tacrolimus and a short course of MTX. Engraftment was confirmed on day 21, and the patient obtained and continued in CR without GVHD.

On day 150 after the second allo-BMT, the patient presented with multiple raised red-brown nodules, widely scattered over his trunk. A biopsy of a skin lesion showed medium-sized blast cells, positive for MPO, CD34 and CD45, which were consistent with AML infiltrates in the skin (Fig. 2). The bone marrow aspirate remained normocellular, with normal maturation of all three lineages and the second donor-derived pattern. CT scans of the whole body showed...
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transformed after the second round intensive chemotherapy of relapse. The surviving leukemic cells might have and did not exhibit EM involvement at the initial presenta-
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by the FAB classification (1, 7). The present patient with 
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leukemic cells such as neural adhesion molecule NCAM 
factor may be associated with the intrinsic properties of the 
lapse of AML after allo-HSCT have been suggested. One 
Isolated EM relapse is usually accompanied by bone marrow 
occurs in the bone marrow where the leukemic burden is the 
cancer therapy; however, the skin lesions expanded rapidly 
patient developed a left facial nerve paralysis. His cerebrospi-
GVL effect; however, his skin lesions expanded rapidly 
without developing any signs of GVHD. Thereafter, the pa-
patient died shortly after the documentation of CNS involve-
EM relapse following allo-HSCT is extremely difficult because of the cumulative toxicities of the 
previous high-dose chemo-radiotherapy and immunosuppres-
sion caused by GVHD and/or immunosuppressants adminis-
tered. Most patients, including even the younger ones, can-
tolerate aggressive systemic chemotherapy and conven-
tional conditioning regimen followed by a second allo-
Thus, physicians should note that AML relapse cannot manage leukemic relapse, and these pa-
tients usually develop overt leukemia. Patients who have not 
suffered from GVHD may be offered discontinuation of im-
munosuppression and donor lymphocyte infusion (DLI) ther-
py to augment the GVL effects; however, data on the effi-
cacy of DLI in patients with isolated EM relapse post allo-
HSCT has not yet shown encouraging results (7, 15). Fur-
thermore, the patient had histories of invasive pulmonary as-
pergilosis and pulmonary abscess. Based on these observa-
tions, in this case we performed a second allo-BMT with the 
RIC regimen from another donor at the documentation of 
EM relapse following the first allo-BMT to gain another 
GVL effect different from that of the first donor. Unfortu-
nately, 5 months later he again developed isolated EM relapse 
confined to the skin and CNS without marrow disease. 
In this case, the AML relapse occurred in EM sites that 
might be inaccessible to chemotherapy and/or the GVL ef-
effect, while a full hematopoiesis from the donor was retained 
in his marrow where the GVL effect could have functioned 
well after the second allo-BMT. In addition, the prolonged 
immunosuppression by the double allo-BMT might impair 
the imunosurveillance against the residual leukemic cells. 
Thus, physicians should note that AML relapse can occur in 
isolated EM sites because the GVL effect might not be uni-
formly effective throughout the body and the surviving leu-

Discussion

AML eventually relapses in 20% to 50% of AML patients 
after allo-HSCT. AML relapse following allo-HSCT usually 
occurs in the bone marrow where the leukemic burden is the 
heaviest, but isolated EM relapse can be detected rarely (1). 
Isolated EM relapse is usually accompanied by bone marrow 
relapse within 1 year, and is known to be a very poor prog-
nostic factor, compared to that of medullary relapse after allo-
HSCT (1, 6, 12). Thus, isolated EM relapse in AML is an 
increasingly recognized cause of treatment failure after 
allo-HSCT.

Predisposing factors that may contribute to the EM re-
lapse of AML after allo-HSCT have been suggested. One 
factor may be associated with the intrinsic properties of the 
leukemic cells such as neural adhesion molecule NCAM 
(CD56) expression, chromosomal aberrations, which include 
t(8; 21), inv (16), and MLL rearrangement, and M4 and M5 
by the FAB classification (1, 7). The present patient with 
AML-M1 did not have these risk factors for EM disease, and 
did not exhibit EM involvement at the initial presenta-
tion of relapse. The surviving leukemic cells might have 
transformed after the second round intensive chemotherapy 
followed by allo-BMTs, and have acquired the ability to ad-
here to dermal fibroblasts, facilitating their binding to EM 
tissues other than the bone marrow stroma, leading to the 
multiple isolated EM relapses (7, 13).

As another possible explanation, the EM sites might serve 
as sanctuary sites for the dormant leukemic clone after allo-
HSCT, since the effect of anti-cancer drugs and/or immune 
cells and cytokines can be diminished in the EM sites due 
to the presence of a barrier (2, 7). Thus, following allo-
HSCT, when the leukemic cells are still sensitive to the 
GVL effect, they may be suppressed in the marrow, but may 
escape from the immnosurveillance in the EM sites where 
the GVL may be less uniformly effective.

There is no established treatment strategy for EM relapse 
post allo-HSCT but experience has shown that the vast ma-
ority of patients with isolated EM relapse subsequently de-
velop marrow disease and have a poor prognosis and rapidly 
succumb to their disease (1, 6, 7). This indicates that a 
small fraction of leukemic cells might be present in the 
bone marrow even in those patients in whom extramedullary 
disease appears to be isolated. To eliminate the residual leu-
Kemic cells resistant to prior therapies throughout the entire 
body, an aggressive treatment with chemotherapy plus a sec-
ond allo-HSCT from another donor should be considered in 
some selected cases, especially in younger patients. How-
ever, the treatment of EM relapse post allo-HSCT is ex-
tremely difficult because of the cumulative toxicities of the 
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tients usually develop overt leukemia. Patients who have not 
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Figure 2. Biopsy specimen of skin lesions on chest demon-
strating infiltration of leukemia cells. Original magnification 
was × 400 (Hematoxylin & cosin stain).
Kemic cells might acquire affinity to the EM sites as a consequence of transformation following allo-HSCT.

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References


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