CASE REPORT

Isolated Breast Relapse of Acute Lymphoblastic Leukemia After Allogeneic Hematopoietic Stem Cell Transplantation

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Abstract Isolated breast relapse after allogeneic hematopoietic stem cell transplantation (allo-HSCT) is less often seen. Chronic graft-versus-host disease (cGVHD) is effective in preventing marrow relapse, but cGVHD seems not to be effective extramedullary relapse (EMR). We report the case of isolated breast relapse after first allo-HSCT for acute lymphoblastic leukemia (ALL). A 47-year-old female was diagnosed with ALL achieved complete remission with salvage chemotherapy and underwent allo-HSCT from an HLA-matched sibling male donor. At 17 months post-transplant, she presented with a bilateral breast masses that confirmed the diagnosis lymphoblast involvement. She had no evidence of leukemia in her marrow that determined 100 % full-donor chimerism when she was relapsed in her both breasts.

Keywords Breast relapse · Stem cell transplantation · Acute lymphoblastic leukemia

Introduction

Allo-HSCT is an effective curative treatment option for high risk or relapsed/refractory ALL. The curative anti leukemia efficacy of allo-HSCT has been contributed to graft versus leukemia (GVL) effect by donor-mediated immune surveillance against leukemic cells [1–3]. It has

been shown that the cGVHD derived from GVL effect is effective in preventing marrow relapse, but may be less effective in preventing EMR. The most frequent sites of extramedullary sites in ALL are the central nervous system (CNS) and the testicles that known as “sanctuary sites”. Besides, it can be seen in any part of the body [3, 4]. Isolated breast relapse is rarely seen and predominantly occurs females.

The optimal treatment regimen of EMR after allo-HSCT remains unclear. Treatment regimens include chemotherapy, localize radiotherapy, donor lymphocyte infusion (DLI) and second allo-HSCT or combined therapies. The prognosis of EMR is controversial compared than BM relapse. Herein, we present a case of 47-year-old female who relapsed an isolated EMR in the both breasts 17 months after an allo-HSCT in ALL.

Case Report

A 47-year old female was diagnosed preB-ALL after examining due to leukocytosis and thrombocytopenia. At the time of diagnosis, hemoglobin was 10.5 g/dl, and white blood cells counts were $40,600 \times 10^9/L$ with 80 % blasts and platelet counts were $51,300 \times 10^9/L$. Blast cells in the bone marrow aspirate expressed CD 10, CD 19, CD79a and TdT by using flow cytometry. Conventional cytogenetic examination revealed 46, XX and no chromosomal abnormalities. PCR analysis for t(9,22); t(1,14) were negativ. She was treated induction chemotherapy with ALL CALGB protocol [5]. Refractory leukemia is determined after induction treatment. She received salvage chemotherapy consisting of FLAG-IDA protocol [6]. On day 28 of salvage chemotherapy, she achieved complete remission with no evidence of marrow infiltration. She

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underwent allo-HSCT from an HLA and ABO-blood group matched sibling male donor (sex mismatch) during her first complete remission after 5 months at diagnosis. Conditioning regimen consisted of 1200 cGy total body irradiation and cyclophosphamide (120 mg/kg). A peripheral blood with a cellular content of CD34: 5.7×10^5 cells/kg was given. Her post-transplant period was complicated by grade 1 acute GVHD involving skin which was treated with corticosteroid. Follow-up, she was developed grade 2 cGVHD with gastrointestinal tract which also was treated with corticosteroid with good response. Seventeen months after allo-HSCT she was admitted with a bilateral multiple painful palpable masses that progressively had been increasing in a period of 2 months. Physical examination revealed a tender, firm and mobil masses in both breast with enlarged bilateral axillary lymph nodes. Breast ultrasonography showed a hypoechoic homogeneous solid masses that was the largest mass measuring 3×5 cm with prominent hypervascularity detected at Doppler USG. Additionally, left breast skin that was suggesting skin involvement was thick and edematous. PET/CT confirmed multiple increased FDG foci within the bilateral breasts and bilateral axillary lymph nodes (SUVmax:7,7–12,5) (Fig. 1).

Fig. 1 a, b PET/CT showed multiple lesions with increased FDG activity within the bilateral breasts and the bilateral axillary lymph nodes

Tru-cut biopsy of breast mass was performed. The microscopic examination showed diffuse infiltration by atypical lymphoblasts among breast ducts (Fig. 2). On immunophenotyping, lymphoblasts were positive for CD 10, CD 19, CD79a and TdT (Fig. 3). Chimaerism analysis revealed complete chimaerism (100 % donor type) at time of breast relapse.

There was no blast in the peripheral blood smear. Bone marrow and cerebrospinal fluid examination revealed no evidence lymphoblast involvement. Cranial MRI showed normal. She underwent salvage chemotherapy HyperC-VAD. Unfortunately, the patient died of intracranial hemorrhage and sepsis at 21 days after starting chemotherapy.

Conclusion

Isolated EMR of acute leukemia after allo-HSCT is seen 21–25 % of all leukemia relapses [4, 7]. Isolated EMR of cumulative incidence of overall relapse after allo-HSCT is 3.1–4.9 % [4, 8]. EMR of ALL after allo-HSCT often occur CNS and testes. In addition to, the other EMR sites including breast, bone, skin and soft tissue and serosa have been reported [7, 9].

In one retrospective study that was documented first EMR after transplantation for acute leukemia reported breast relapse in 15 patients of ALL between ages 11 and 31. Except for one patient, all patients were female. Six patients had prior or simultaneous in marrow relapse. All breast relapses occurred within 24 months of after transplantation [10]. In our patient was older than patients of this study. Our patient had developed breast relapse within the first 24 months after transplantation.

Fig. 2 Microscopic examination reveals atypical lymphoblasts along with epithelial cells of breast (hematoxylin and eosin stain, $\times 200$)

Fig. 3 Atypical lymphoblasts are strongly and diffusely positive for CD10 (CD10 immunostain $\times 100$)

Female gender is an important risk factor for breast relapse after HSCT [10]. The other risk factors for EMR including breast after allo-HSCT are not well defined that include acute leukemia subtype, disease status at the of transplant, presence of cGVHD, hyperleukocytosis, high risk patients for cytogenetics [8, 11]

It is noteworthy that EMR occur later than marrow relapse [4, 11]. Additionally, the presence of cGVHD that is derived from GVL effect is protective against bone marrow relapse, but is not effective against EMR [7, 8]. Taken together, this findings suggest that the pathogenetic mechanism of EMR after allo-HSCT differ from that of marrow relapse. In our patient's had previously grade 1 cGVHD, complete donor chimerism and no evidence of relapse in marrow when she had breast relapse. Similarly, there were two cases of breast relapse after allo-HSCT in B-ALL that described cGVHD, complete donor chimerism and no marrow involvement [12, 13].

Optimal therapeutic approaches are not yet defined. These approaches include surgery, RT, CT, DLI or second HSCT and combined therapy. Fadilah et al. demonstrated 18-year-old female who revealed bilateral masses both in the breasts and ovaries after allo-HSCT in B-ALL. The breast mass of histologic examination confirmed B-ALL without marrow involvement. The patient treated radiotherapy of the breasts and systemic chemotherapy, followed DLI, resulting a near—complete remission of the breast masses and a total resolution of the ovarian masses. The patient was alive and free of disease 10 months after the onset of relapse in the breast. Cunnigman reported that 15 patients are seen breast relapse with or without marrow involvement after allo-HSCT in ALL. One patient received alone chemotherapy and relapsed in the breast. In six patients who treated RT alone, one patient died and five

patients relapsed. Four patients with treated RT plus chemotherapy who achieved remissions, developed relapses. Four patients were treated DLI that was part of combine therapy. After other treatments, four patients underwent second transplant. One died of toxicity and three relapsed in bone marrow.

Generally, prognosis of EMR after allo-HSCT is poor. But, some studies showed that isolated EMR after allo-HSCT is associated with a better survival than medullary relapse when intensive treatment is provided [14, 15]. Solh et al. showed that patients who received systemic or combined modality therapy for the EM relapse had better overall survival compared with those treated with local therapy only. In other studies, better survival advantage has not been supported [16, 17]. There was no significant difference in survival among patients with isolated EMR compared with combined BM/EM relapse or isolated BM relapse [11, 16].

In conclusion; increased allo-HSCT and salvage DLI; and prolongation of survival after allo-HSCT, the incidence of EMR should be expected to occur more frequently. It should be kept in mind that breast relapse may occur after allo-HSCT in ALL patients especially, young or premenopausal women. The prognosis of isolated EMR after allo-HSCT is usually dismal, although is controversial. Better results is shown by intensive systemic treatment. However, most patients who develop EMR have been previously treated with intensive chemotherapy and with intense immunosuppression for GVHD, thus treatment-related toxicity and mortality increased. cGVHD is not effective preventing EMR. Factors that may be effective in preventing relapse EMR is still unclear.

Conflict of interest The authors report no declarations of interest.

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