Stem Cell Transplant for Juvenile Myelomonocytic Leukemia and Chronic Myelomonocytic Leukemia

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Abstract Juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML) are myelodysplastic/myeloproliferative neoplasms associated with poor prognosis. There is no definitive treatment for such patients other than stem cell transplantation, and chemotherapy is not much effective. Timely diagnosis and early referral to the transplant centre is important for the management of these diseases. We report here a case of JMML and another case of CMML who were treated successfully with peripheral blood stem cell transplantation.

Keywords Juvenile myelomonocytic leukemia · Chronic myelomonocytic leukemia · Stem cell transplantation

Introduction

Juvenile myelomonocytic leukemia (JMML) and chronic myelomonocytic leukemia (CMML) are rare hematological malignancies that are classified by the World Health Organization (WHO) as ‘myelodysplastic/myeloproliferative (MDS/MPN) diseases’ and are associated with poor prognosis [1, 2]. JMML is most commonly diagnosed in infants and children younger than 6 years. Child presents with pallor, decrease in appetite, irritability, rash, hepatosplenomegaly and lymphadenopathy. JMML accounts for 2–3 % of childhood leukemia cases [3, 4]. A persistent elevated monocyte count in the blood ($>1 \times 10^9/l$), the absence of the Philadelphia chromosome and the BCR-ABL gene rearrangement and less than 20 % blasts in the blood or bone

marrow are diagnostic of JMML [1, 2]. CMML is a similar disorder but has later age of onset. For CMML, the median age at diagnosis ranges from 65 to 75 years. Patient commonly presents with weakness, fatigue, bleeding manifestations, infection and enlarged liver or spleen. WHO diagnostic criteria for CMML includes persistent peripheral blood monocytosis ($>1 \times 10^9/l$). There should be no Philadelphia chromosome or BCR-ABL fusion gene, no rearrangement of PDGFRA or PDGFRB, and less than 20 % blasts in the blood and bone marrow. Dysplasia may be present in one or more myeloid lineages and there may be an acquired clonal cytogenetic or molecular genetic abnormality [1]. Allogeneic stem cell transplantation is the only potentially curative treatment for both JMML and CMML.

Case Presentation

Case 1

A 5-year-old boy was admitted with low grade fever, weakness and lump in the left hypochondrium for 1 month. On evaluation he was found to have hemoglobin of 8.6 g/dl, high leukocyte count ($35 \times 10^9/l$) with monocytosis (21 %, absolute monocyte count $7.3 \times 10^9/l$), platelet counts $56 \times 10^9/l$, lymphadenopathy and hepatosplenomegaly. Bone marrow aspiration and biopsy showed dysmyelopoiesis with monocytosis and 3 % blasts. His HbF was raised (30.5 %). Philadelphia chromosome and the BCR-ABL gene rearrangement were not detected. He was diagnosed as JMML and was given 3 + 7 induction with daunorubicin (60 mg/m^2 for 3 days) and cytarabine (100 mg/m^2 for 7 days continuous intravenous infusion) which resulted in normalization of his total and differential counts and regression of spleen. There was no HLA matched sibling but he had 5/6 match with his

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mother and was taken-up for myeloablative peripheral blood stem cell transplant with conditioning regimen including busulfan (3.2 mg/kg/day intravenously for 4 days) and cyclophosphamide (60 mg/kg/day for 2 days), and mother as donor. CD34+ stem cell dose was 13×10^6 /kg. Graft versus host disease (GvHD) prophylaxis included methotrexate (15 mg/m² on day 1, and 10 mg/m² on day +3, +6 and +11) and cyclosporine (1.5 mg/kg twice daily intravenously, and later orally, with trough plasma cyclosporine levels maintained between 200–350 ng/ml). On day +9 child developed hyperacute GvHD with diffuse erythematous skin rash (grade III–IV) which responded to intravenous methylprednisolone (2 mg/kg/day), followed by oral prednisolone. Patient engrafted on day +14. Two months post transplant patient had grade II skin GvHD which required steroids and mycophenolate mofetil. Three months post transplant patient has normal differential count, no lymphadenopathy and hepatosplenomegaly, 100 % donor chimerism and mild skin GvHD.

Case 2

A 47-year-old woman was admitted with weakness, low grade fever and bleeding manifestations for 2 months duration. Hemogram showed hemoglobin 8 g/dl, total leukocyte count 21.6×10^9 /l with 17 % monocytes (absolute monocyte count 3.7×10^9 /l) and platelets 0.3×10^9 /l. Bone marrow aspiration and biopsy showed granulocytic marrow with dysgranulopoiesis, reduced number of megakaryocytes and prominence of monocytes, blasts were less than 5 %. No Philadelphia chromosome, BCR-ABL fusion gene or rearrangement of PDGFRA or PDGFRB was noted. Karyotyping showed normal cytogenetics. Computed tomography revealed retroperitoneal lymphadenopathy. She had a sibling matched donor and was taken up for peripheral blood stem cell transplantation with reduced intensity conditioning regimen including fludarabine (30 mg/m² from day –6 to day –2) and melphalan (140 mg/m² on day –1). CD34+ stem cell dose was 5.65×10^6 /kg. GvHD prophylaxis included cyclosporine (1.5 mg/kg twice daily intravenously, and later orally, with trough plasma cyclosporine levels between 200–350 ng/ml) and methotrexate (5 mg/m² on day +1, +3 and +6). Patient engrafted on day +11. She developed acute gut GvHD on day +16 and was treated with intravenous methylprednisolone 2 mg/kg which resulted in complete remission of gut GvHD. Three months post transplant patient has 99.3 % chimerism and complete disappearance of retroperitoneal lymphadenopathy.

Discussion

JMML is a rare hematopoietic neoplasm of early childhood, representing 2–3 % of all pediatric leukemias and is

associated with poor prognosis [2–4], with about one-third of patients developing a rapidly progressive fatal disease [3, 4]. The 10-year disease-free survival without stem cell transplantation has been reported about 6 %, with median survival ~10 months [4–7]. Chemotherapy has not been much successful in these types of leukemias, with only partial response to even high-dose chemotherapy protocols [4–7]. Allogeneic hematopoietic stem cell transplantation (HSCT) is the only curative therapy for JMML with potential for graft-versus leukemia (GVL) effect resulting in lower relapse rates [8, 9]. The European Working Group on Childhood MDS (EWOG-MDS) and the European Blood and Marrow Transplantation (EBMT) Group, reported that HSCT either from related or unrelated donor, after a preparative regimen consisting of busulfan, cyclophosphamide, and melphalan may cure ~50 % of patients with JMML [10].

Similarly, an allogeneic SCT is the only treatment option for patients with CMML that can maintain a long-term remission and offer a cure to some patients [11]. In a study from Fred Hutchinson Cancer Center, 77 patients (91 %) with CMML achieved sustained engraftment after HSCT and ten-year relapse free survival was 40 % [12]. Both of our patients engrafted. Though both had acute GvHD, it was successfully managed. After a median follow-up of 3 months both patients are in remission with nearly 100 % chimerism.

Conclusion

JMML and CMML are a group of rare hematological malignancies with poorer prognosis. Chemotherapy has not been found to be effective in these disorders and the only definitive way to replace the leukemic clone is by allogeneic stem cell transplantation. With improved conditioning regimens, immunosuppressive therapies and supportive care, increased survival of patients with JMML and CMML can be expected. Timely diagnosis and early referral to the transplant centre is important for the management of these diseases.

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