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## Case Report and Review of the Literature

# Hematopoietic Stem Cell Transplantation in Juvenile Myelomonocytic Leukemia: A Case Report and Literature Review

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ABSTRACT

Juvenile myelomonocytic leukemia (JMML) is a rare hematological malignancy of early childhood, classified by the World Health Organization as a myelodysplastic/myeloproliferative disease and is associated with a poor prognosis. Allogeneic hematopoietic stem cell transplantation is the only curative treatment. A two-year-old male child was diagnosed with JMML and was given induction chemotherapy. One year after diagnosis, the patient received allogeneic hematopoietic stem cell transplantation from an HLA sibling donor after a myeloablative conditioning regimen. The patient remained free of disease after 5 years of follow-up, healthy, with complete clinical, immunologic and hematologic recovery, without signs of JMML. Transplantation is the only modality to achieve a cure in JMML patients. The most widely practiced approach is the use of bone marrow or peripheral blood stem cells after a myeloablative conditioning regimen. Post-transplant monitoring chimerism can help identify the patients who are at risk of relapse.



## Introduction

Juvenile myelomonocytic leukemia (JMML) is a rare hematological malignancy of early childhood representing 2 to 3% of all pediatric leukemia cases; classified by the World Health Organization (WHO) as a myelodysplastic/myeloproliferative disease and is associated with poor prognosis. Allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment [1-3].

## Case Presentation

A two-year-old male child presented with pallor, fever, skin rash and pain in the abdomen for three weeks. The patient had no similar complaints in the past. The birth history was normal. The patient was fully vaccinated and had normal developmental milestones. He had cervical lymph nodes of size ranging between 1 to 2 cm. The spleen and liver were palpable 4 and 3 cm below the costal margin, respectively. CT-scan revealed abdominal lymphadenopathy and hepatosplenomegaly. No significant abnormality was seen with the X-ray thoracic chest. Complete blood cell count showed leukocytosis ($31.8\times10^9$/L), anemia (8.9 g/dL), normal platelet counts ($368\times10^9$/L) and absolute monocyte count ($7.9\times10^9$/L). Morphologic evaluation of peripheral blood smear noted a myelemia with 10% of myelocytes, metamyelocytes, and erythroblasts. Bone marrow (BM) aspiration showed hypercellularity with dysgranulopoiesis and 4% blasts. No BCR-ABL fusion transcript was found and karyotype on BM cells shows trisomy 8. The synthesis of fetal haemoglobin (HbF) was 0.2%. Abnormal JMML-related mutations were not done. He was diagnosed as JMML and was given induction chemotherapy with cytarabine (25 mg/m$^2$/d) and Mercaptopurine (50 mg/m$^2$/d), 5 days/month, 8 courses, with resulted in regression of hepatosplenomegaly and normalization of his total and differential counts.

One year after diagnosis, the child received peripheral blood stem cell (PBSC) as a graft (CD 34 cell counts: $8.7\times10^6$/kg) from an HLA sibling donor after a conditioning regimen associated with Busilvex and Ciclophosphamide (200 mg/kg) and GVHD prophylaxis with cyclosporin and methotrexate. The time required for achieving a

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granulocyte count greater than $0.5\times10^9$/l was 22 days. No complications noted: severe infection, cytomegalovirus (CMV) reactivation, acute or chronic graft versus host disease (GVHD). Chimerism was fully donor (> 95% donor) at days +30, +100, +180 and +365 posttransplant. The patient remained free of disease after 5 years of follow-up, healthy, with normal growth, complete clinical, immunologic and hematologic recovery, without signs of JMML.

## Discussion

JMML has a peak incidence at the age of 2 years and patients present with various symptoms that could also be associated with infection. The diagnostic criteria of JMML are presented in (Table 1). The common clinical symptoms include fever, coughing, lymphadenopathy, hepatosplenomegaly, cutaneous lesions and skin bleeding. Usually, a blood examination shows high white blood cell counts, anaemia, thrombocytopenia, monocytosis and elevated haemoglobin F. Myeloid precursors are found in the morphologic evaluation of peripheral blood smear and the percentage of blasts in peripheral blood and bone marrow is lower than 20%. Monosomy of chromosome 7 is the most frequent karyotypic abnormality and more than 85% of the patients have a mutation in *K-RAS*, *N-RAS*, *PTPN-11*, *CBL* or *NF1*, causing aberrant activation of the RAS signalling pathway and GM-CSF-hypersensitivity [1, 4, 5].

**Table 1:** The diagnostic criteria for JMML (2016 WHO classification).

| |
|---|
| **I. Clinical and hematologic features (all 4 features mandatory)** |
| - Peripheral blood monocyte count $\geq 1.10^9$/L |
| - Blast percentage in peripheral blood and bone marrow < 20% |
| - Splenomegaly |
| - Absence of Philadelphia chromosome (BCR/ABL rearrangement) |
| **II. Oncogenetic studies (1 finding is sufficient)** |
| - Somatic mutation in PTPN11 or K-RAS or N-RAS * |
| - Clinical diagnosis of NF-1 or germline NF1 mutation |
| - Germline CBL mutation and loss of heterozygosity of CBL** |
| **III. For patients without any oncogenetic parameter, besides clinical and hematologic features listed under I, the following criteria must be met:** |
| - Monosomy 7 or any other chromosomal abnormality or at least 2 of the following criteria: |
| - HbF increased for age |
| - Myeloid or erythroid precursors on peripheral blood smear |
| - Spontaneous growth or GM-CSF hypersensitivity in colony assay |
| - Hyperphosphorylation of STAT5 |

WHO: World Health Organization. * Germ line mutations (indicative of Noonan syndrome) need to be excluded.

** Occasional cases may harbor heterozygous splice site mutations. NF-1: Neurifibromin-1; CBL: Casitas B-lineage lymphoma; PTPN11: Protein Tyrosine Phosphate Non-Receptor type; K-RAS: Kristen Rat Sarcoma; N-RAS: Neuroblastoma Rat Sarcoma.

In the majority of cases, JMML is a fatal disorder in children who do not receive transplantation. Allo-HSCT is the only curative modality in JMML. It has been recognized that patients with germline CBL and acquired loss of heterozygosity or biallelic *CBL* mutations may not require HSCT. In contrast, patients with JMML and *NF1*, somatic *PTPN11* or *KRAS* mutation, the majority of somatic NRAS and those without known molecular lesions have a clear indication for HSCT [3, 6, 7]. Stieglitz *et al*. demonstrate that patients who harbor two or more somatic alterations at diagnosis had significantly worse EFS and OS compared to those with one or fewer events [8]. Therapeutic considerations range from observation to allo-HSCT, depending on the genetic subtype. Initial diagnosis at the age of > 2 years old, platelet count $\leq 33\times10^9$/L, Haemoglobin F level > 10%, chromosome 7, *PTPN11* mutations and combined gene mutations have been recognized as the main predictors of short survival in JMML [4, 8, 9].

The standard conditioning regimen for JMML, as originally proposed by the European Working Group of Myelodysplastic Syndromes (EWOG-MDS) in childhood, is the Busulfan-Cyclophosphamide-Melphalan (BU-CY-MEL) regimen who achieved a 52% rate of long-term disease-free survival [10]. Myeloablative conditioning regimen (MAC) with Total Body irradiation (TBI) has no benefit and suggests that among regimens without TBI, BU-MEL with Fludarabine (FLU) could be a standard conditioning regimen in addition to the conventional BU-CY-MEL. A randomized study that compared the potentially less toxic FLU-BU with the standard BU-CY-MEL regimen was quickly closed due to the high incidence of relapse and the extremely low probability of EFS in the FLU-BU arm. One report of 10 children given orally BU, FLU (120 mg/m$^2$), and MEL (180-210 mg/m$^2$) demonstrated promising results, with 7 patients in remission > 2 years since HSCT. Martenson *et al*. compared two different conditioning regimens and concluded that the addition of MEL to the BU-CY conditioning regimen resulted in severe gastrointestinal complications and did not improve overall survival. Like our patient, the most widely practiced approach is the use of BM or PBSC after MAC with alkylating drugs which appears potentially capable of eradicating stem cell disorders, such as JMML [3,10-18].

Retrospectives studies indicate that an unrelated donor (UD) offers minimal or no significant disadvantage compared with using an HLA-identical sibling and using an umbilical cord blood transplant (UCBT) have similar outcomes to that reported with different sources of HSC. A recent study suggested similar rates of acute and chronic GVHD and non-relapse mortality in mismatched haploidentical donor transplants compared to matched donors [5,18].

GVHD prophylaxis consisted of association of Cyclosporin and Methotrexate in our patient. This procedure is most commonly employed. The risk of transplant-related mortality (TRM) is approximately 13% and disease recurrence remains the major cause of treatment failure, with a higher probability of relapse (30% to 60%) within the first year [5, 12]. Chronic GVHD is an independent factor associated with a lower incidence of relapse and a higher probability of survival, suggesting the importance of graft versus leukemia (GVL) effects in JMML following HSCT [9, 11, 16-19]. Furthermore, grade 2-3 acute GVHD was associated with decreased incidence of relapse in the EUROCORD-CIBMTR (Center for International Blood and Marrow Transplantation Research) study [5].

Our patient is considered in complete remission according to the criteria proposed by Niemeyer *et al*. The remission criteria include the results of chimerism analyses. Patients who achieve neutrophil engraftment and complete donor chimerism with the disappearance of acquired cytogenetic and molecular abnormalities are considered to have a complete remission of JMML [20]. In several cases of mixed chimerism (MC), withdrawal of immunosuppressive therapy induced complete chimerism after allo-HSCT [19]. In the absence of acute GVHD, prophylaxis should be discontinued between day 60 and day 90. Donor lymphocyte infusion (DLI) is not effective for patients with MC or relapse, second allo-HSCT from either the same or different donor, should be considered [3, 5, 10, 19-22]. The clinical activity and acceptable toxicity of Azacitidine (32 mg/m$^2$/day for 5 days, every 4 weeks), provide a rationale for its use in cases where allo-HSCT has failed, as a bridging strategy to second transplantation [22, 23]. Age > 4 years, BM blasts > 20% have been found to be associated with an increased risk of relapse [10].

A variety of pre-transplant treatments have been employed to control symptoms of JMML. Low-dose intravenous cytarabine alone or in combination with 6-mercaptopurine, and high-dose cytarabine have been used. No standard chemotherapy protocol has proven to have an impact on relapse incidence after transplantation but the favourable toxicity of azacitidine (75-100 mg/m$^2$ on 5 to 7 days, repeated every 4 weeks) and its cytoreductive potential make it an attractive option prior to allo-HSCT [12, 24-26]. Patients with JMML who transform into acute myeloid leukemia (AML) generally have dismal outcomes following HSCT [10, 27]. An EWOG-MDS/EBMT trial reported no significant differences in terms of EFS (52% vs. 50%), relapse incidence (35% vs. 38%), or TRM (13% vs. 13%) between AML-type chemotherapy and less intensive treatment. The same group indicates that spleen size at the time of transplantation and splenectomy prior to transplantation does not appear to have an impact on outcome [10]. A recent study noted better post-HSCT outcome of patients who experienced molecular response to pretransplant treatment [28].

## Conclusion

Allo-HSCT is the only modality to achieve a cure in JMML patients. Azacytidine is a promising agent in recent clinical trials to achieve hematological and molecular responses in some patients with the aim of reducing the burden of disease before HSCT. The most widely practiced approach is the use of BM or PBSC after high-intensity MAC. Post-transplant monitoring chimerism can help identify the patients who are at risk of relapse.

## Conflicts of Interest

None.

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