Juvenile Myelomonocytic Leukemia in India: Cure Remains a Distant Dream!

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Abstract There is paucity of outcome data regarding juvenile myelomonocytic leukemia from India. We report a series of eight children. Three had monosomy 7 and one had complex cytogenetics. One with Down's syndrome recovered spontaneously. Three refused therapy of whom only one is alive with disease. One died post chemotherapy. Three underwent allogeneic stem cell transplant after protracted delay with funds arranged from various governmental and non-governmental organizations. Of these two died (relapse-1 and intracranial bleed-1) and one is alive and disease free. In India, it's a milestone to reach transplant due to high cost and cure still remains a distant dream.

Keywords JMML · HSCT · Hydroxyurea

Introduction

Juvenile myelomonocytic leukemia (JMML) is a rare, unique clonal hematopoietic disorder of early childhood

characterized by excessive proliferation of the monocytic and granulocytic lineages leading to high morbidity and mortality [1, 2]. Diagnostic criteria were initially proposed by International JMML Working Group [3]. Identification of NF-1, Ras, PTEN mutations and monosomy 7 also helps [4]. Conventional chemotherapy rarely achieves cure [1]. However, survival up to 57–64 % have been reported post allogeneic stem cell transplant (SCT) [5, 6]. There is a paucity of outcome data for JMML from India [7–9].

Materials and Methods

We retrospectively reviewed inpatient and outpatient records of children diagnosed with JMML at our hospital from Jan05 to July12. The diagnosis of JMML was based on criteria of International JMML Working Group [3].

Results

Among 400 newly-diagnosed children with leukemia, eight had JMML (male-5 and female-3). All except two were infants. The time lapse between the onset of symptoms and diagnosis varied from 2 to 8 months (mean 3.5 months). The presenting symptoms were fever, abdominal distension and/or bleeding. All had splenohepatomegaly and a few had lymphadenopathy and/or edema. One patient also had Down's syndrome.

The hematological data are summarized in Table 1. Three patients had normal karyotype on bone marrow chromosomal analysis; while three had monosomy 7 and one had complex cytogenetics as depicted in Table 2. BCR–ABL by PCR was negative in all cases.

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Table 1 Hematological parameters in eight children with JMML

Parameter	Mean	Range
Hb (g/dl)	8.43	5.5–12.2
WBC ($10^9/L$)	58.28	27.7–103
Platelets ($10^9/L$)	37.25	15–66
Immature granulocytes (PB)	14	5–35
Blasts % (PB)	6	1–12
AMC ($10^9/L$) (PB)	10.07	3.6–18.6
Normoblasts % (PB)	7.75	1–20
M:E ratio (BM)	11.75:1	5:1–25:1
Monocytes (BM)	10	2–26
Blasts % (BM)	8	4–10
Fetal hemoglobin %	6.94	1.2–20

AMC absolute monocyte count, PB peripheral blood, BM bone marrow

Clinical features and outcome data are described in Table 2. The child with Down's syndrome recovered spontaneously after 6 months. The parents of three children refused treatment due to high cost. Of these two have died and one child is alive on hydroxyurea. One patient who received low dose intravenous cytarabine, died due to tumor lysis syndrome. Hydroxyurea (25–30 mg/m²/day) was used as a bridge to SCT until funds could be arranged in the remaining three patients. All three underwent SCT (two at our centre and one at another centre). Of these one is alive and disease free. Here we describe details of the two patients who underwent SCT at our centre.

Case 1 An 11-month-old was diagnosed with JMML. Ten months after diagnosis, she underwent matched sibling donor peripheral blood SCT. She was conditioned with oral busulfan (16 mg/kg), cyclophosphamide (120 mg/kg), and melphalan (140 mg/m²). graft versus host disease (GVHD) prophylaxis consisted of cyclosporine alone. Peripheral blood stem cells (5.3 million/kg of the recipient) were infused on day 0. Her neutrophil and platelets engrafted on day + 22 and day + 70 respectively. She remained transfusion independent for 11 months, subsequently relapsed and died.

Case 2 An 8-month-old male was diagnosed with JMML. Thirteen months from diagnosis he developed massive splenomegaly needing emergency splenectomy. Finally, after arranging funds from governmental and non-governmental agencies, he underwent unrelated double cord blood transplant (CBT) at the age of 2 years. He received the same conditioning as the first case. Both cord units were 4/6 matched with the recipient and 6/6 with each other. The combined CD34 cell count of the two grafts was

$2.69 \times 10^5/kg$ of recipient body weight. GVHD prophylaxis comprised of ATG, cyclosporine and prednisolone. His neutrophil and platelets engrafted on day + 15 and day + 49 respectively. He developed grade-III acute skin and gut GVHD which was controlled with steroids and topical medications. It later evolved into a chronic skin rash and diarrhea. The peripheral blood chimerism showed 100 % donor cells with persistence of both cord units. On day + 320 he had a recurrence of acute skin and gut GVHD and developed thrombocytopenia. He reached hospital with intracranial bleed and could not be revived.

Discussion

JMML is a rare disorder and since it occurs in very young infants, decisions by parents are often delayed. In our series treatment refusal was a significant problem and arranging funds for SCT was a challenging task which was made possible with donations from various governmental and non-governmental agencies. Due to cost constraints we decided to observe our patient with Down's syndrome and he achieved spontaneous remission without any therapy. Only one previous case of JMML and Down's syndrome has been described [7]. However spontaneous resolution has not been described. It is possible that it was transient abnormal myelopoiesis.

There are few reports of JMML from India [8–10]. But outcome data are lacking. The JMML patients rarely achieve a remission with intensive chemotherapy regimens alone, and if they do achieve a remission it is short-lived [1]. Both patients who received chemotherapy died (one at our centre and second at another centre). The only curative therapy is allogeneic SCT which is able to cure ~50 % of patients [5, 6]. There are no reports of SCT for JMML from India and in our series three children successfully underwent allogeneic SCT. The leading cause of death following transplantation continues to be leukemia relapse [5]. One of three transplanted children relapsed in our series.

Cord blood is an important alternative stem cell source in young patients without a suitable bone marrow donor. A recent retrospective study by the European Blood and Marrow Transplant (EBMT) and European Working Group (EWOG) myelodysplastic syndrome (MDS), which enrolled 42 patients with JMML, showed that the 2 year disease-free survival was 45 % after unrelated CBT [11]. Our patient was disease-free at 11 month post-CBT however developed recurrence of acute GVHD of skin and gut with severe thrombocytopenia leading to intracranial bleed and death.

Table 2 Clinical features and outcome of children diagnosed with JMML

Case no.	1	2	3	4	5	6	7	8
Age/sex at diagnosis	11 m/F	11 m/F	8 m/M	8 yr/F	9 m/M	3 m/M	8 m/M	8 yr/M
Liver (cm)	5	5	6	5	6	5	5	5
Spleen (cm)	10	10	10	8	12	6	5	6
WBC ($10^9/L$)	103	45.7	55.3	70.4	80.6	50.4	33.2	27.7
Platelets ($10^9/L$)	47	66	15	28	16	50	43	33
AMC (PB)	18,612	3,656	8,848	12,672	16,120	9,072	6,640	4,986
Blasts % (PB)	3	5	7	5	8	6	13	1
Blasts % (B.M)	5	10	8	8	4	10	8	10
Hb F (%)	1.2	14	1.1	8	2.8	20	4.8	3.6
Cytogenetics	Normal	Normal	Monosomy 7	Normal	46XY,t(1;6)(q11;q16.3), (3)/46XY del(6) (q16.3q27)(10)	Trisomy 21 (Down's syndrome)	Monosomy 7	Monosomy 7
Treatment	Hydroxyurea	Refused	Hydroxyurea, Splenectomy	Refused ^a	Cytarabine	Observation	Hydroxyurea	Hydroxyurea
SCT	Yes (MSD)	No	Yes (Cord)	No	No	No	No	Yes
Outcome	Died	Died	Died	Died	Died	Alive	Alive	Alive
Disease status	1st Relapse	Not in CR	CR1	Not in CR	Not in CR	CR1	Not in CR	CR1
Cause of death	Relapse	Disease	Intracranial bleed	Sepsis	Tumor lysis			
Duration of follow up	21 m	10 m	26 m	2 m	0.5 m	60 m	6 m	10 m

cm centimeter (below costal margin), *m* month, *yr* year, *M* Male, *F* female, *PB* peripheral blood, *BM* bone marrow, *MSD* matched sibling donor, *SCT* stem cell transplant, *CR* complete remission, *Neg.* negative, *AMC* absolute monocyte count

^a Received chemotherapy at another centre

In the developing world reaching SCT for JMML is a milestone. However, cure still remains a distant dream.

Disclosure None of the authors have anything to disclose.

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