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Juvenile Myelomonocytic Leukemia: Experience from a Tertiary Care Hospital in Eastern India

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Background and objective: Juvenile myelomonocytic leukemia (JMML), previously known as juvenile chronic myeloid leukemia, is a rare, aggressive myeloproliferative neoplasm primarily affecting early childhood. Diagnosing JMML can be challenging due to overlapping clinical and hematological features with other myeloproliferative neoplasms (MPNs). However, unique characteristics such as monocytosis, the absence of BCR-ABL translocation, and the presence of specific mutations (PTPN-11, K-RAS, N-RAS, CBL, or NF1) aid in confirming the diagnosis.

Material and methods: This prospective analysis included six JMML patients with varying clinical features treated with injection azacytidine as frontline therapy over a two-year study period.

Results: The median age at diagnosis was 4.5 years, with a male-to-female ratio of 2:4. Pallor and splenomegaly were the most common presenting signs. Four patients (66.67%) achieved complete remission (CR), two patients (33.33%) had partial remission (PR), and one patient (16.67%) experienced progressive disease (PD). The overall survival rate was 66.67% (four out of six), and the mortality rate was 33.33%.

Conclusion: Azacitidine can be an effective treatment option as frontline therapy for JMML, particularly in resource-limited developing countries.

Introduction

JMML is a rare haematological neoplasm accounting for 2–3% of all childhood malignancies and characterised by excessive proliferation of myeloid and monocytic lineages [1]. Males are more affected than females, and the median age of presentation is 2 years, with >90% having mutations

in the RAS signalling pathway [2]. Close differentials include other MPNs, herpes virus infection, leukocyte adhesion defects, hemophagocytic lymphohistiocytosis, infantile malignant osteopetrosis, and wiskott-aldrich syndrome [3]. Diagnosis is made by WHO criteria fulfilling all the four major clinical/ haematological criteria (peripheral blood monocyte count ≥1x10^9/L, blast percentage in peripheral blood and bone marrow <20%, splenomegaly, and absence of philadelphia chromosome (BCR/ABL rearrangement), with either one genetic finding (somatic mutation in PTPN11 or K-RAS or N-RAS or RRAS, germline NF1 mutation and loss of heterozygosity of NF1 or clinical diagnosis of neurofibromatosis type 1, germline CBL mutation and loss of heterozygosity of CBL) [4].

Materials and Methods

This was a prospective analysis of six cases diagnosed as JMML as per the WHO criteria [4], over a study period of two years from March 2021 to February 2023 in the Department of Haematology at Nil Ratan Sircar Medical College and Hospital, Kolkata, India.

In all the cases, morphological evaluation in peripheral blood smears and bone marrow aspiration with biopsy smears was done. Reverse transcriptase Polymerase chain reaction (RT-PCR) for BCR-ABL qualitative assay from peripheral blood proved negative in all the cases, and conventional cytogenetics was done from bone marrow sample. Next-generation sequencing (NGS) was done from peripheral blood only in selected cases due to financial reasons.

All diagnosed JMML patients were included in the study, and those who proceeded with hematopoietic stem cell transplant (HSCT) were excluded from the study. All patients received injection azacytidine @ 75mg/m^2/day intravenously daily for seven days per month as frontline therapy [5]. The Centre for International Blood and Marrow Transplant Research (CIBMTR) guidelines were followed for the determination of JMML response criteria [6].

Results

A total of eight JMML cases were screened during the study period, out of which two proceeded with HSCT and were excluded from the study. Hence, a total of six patients were included in the present study.

All six patients characteristics are summarised in Table 1.

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age (years)/Sex	5/ Female	8/Female	6/ Male	5/Female	1/Female	4/Male
Presentation	Fever, Pallor, Orbital mas	Pallor, Epistaxis	Pallor, abdominal fullness	Fever, Pallor	Pallor, Multiple petechiael spots	Fever, Pallor
Clinical findings	Spleen 4cmCervical LAP	Liver 2cmSpleen 6cm	Liver 10cmSpleen 14 cmCervical and axillaryLAP	Spleen 2cm	Liver 2cmSpleen 2cmCervical LAP	Spleen 4cm
TLC (x 109/l)	78.72	54.56	39.92	124.56	61.24	28.77
Absolute monocyte count ((x 109/l)	16.45	9.92	6.32	24.47	12.34	4.56
Myeloid/eyrthroid precursors in PB	Yes	Yes	Yes	Yes	Yes	Yes
Hb (g/dl)	5	7.8	4	7.5	5.8	9.2
Platelet (x 109/l)	12	38	5	9	45	39
Blasts % (PB/BM)	05-Feb	04-Jan	08-Feb	10-Mar	05-Mar	03-Feb

Dysplastic lineage	Dysgranulopoeisis Dysmegakaryopoeisis	Dysgranulopoeisis	Dysgranulopoeisis	Dysgranulopoeisis Dysmegakaryopoeisis	Dysgranulopoeisis	Dysgranulopoeisis
Cytogenetics	Trisomy 8	Normal	Trisomy 8	Monosomy 7	Trisomy 8	Normal
Molecular profile	NRAS+	NRAS+	NA	NA	NA	CBL+
Chemotherapy cycle	1st cycle azacitidine2nd cycle vincristine+ cytarabine + etoposide	2nd cycle azacitidine	2 cycles azacitidine	1st cycle azacitidine	13 cycles azacitidine/ 13 months	5 cycles azacitidine/ 5 months
Outcome /Follow up	Dead	Alive/ 2 months	Lost to follow up/ 3 months	Dead	Alive	Alive
Response	PD	PR	CR	PR	CR	CR

Table 1. JMML Patient Characteristics (n=6).

The median age was 4.5 years, and the male: female ratio was 2:4.

Fever (50%) and pallor (100%) were the most common presenting complaints, and one patient presented with right eye proptosis (16.67%) (Figure 1).

Figure 1. Clinical and Haematological Features in JMML Patients. 1. A) Case 1 presening as right eye proptosis. 1. B) Peripheral smear from Case 3 patient showing myeloid precursors (PM-Promyelocytes, MY-Myelocytes) along with dysmyelopoeisis in the from of dysplastic neutrophil (DN) and monocytosis (M).

Splenomegaly (100%) was the most common sign, which was present in all the patients. Hepatomegaly and lymphadenopathy (LAP) were present in three out of six patients (50%).

The median total leukocyte count (TLC) was 57.9 x 10^9/l (range 28.77–95.79), and the median absolute monocyte count was 11.13 x 10^9/l (range 4.56–24.47). Anaemia (100%) and thrombocytopenia (100%) were present in all the cases. Dysgranulopoeisis (100%) in bone marrow examination was evident in all six patients, and dysmegakryopoeisis was present in two out of six patients (33.34%).

In the cytogenetic studies, two patients had trisomy 8 (33.33%), and one patient had monosomy 7 (16.67%). NGS could be done on three patients, out of whom two (33.33%) had mutations in the NRAS gene and one (16.67%) had mutation in the CBL gene.

Azacitidine was given to all the patients. Case 1 was unresponsive to azacitidine; hence, a salvage chemotherapy cycle was given with vincristine, cytarabine, and etoposide, during which the patient succumbed to death. Four patients (66.67%) achieved complete remission (CR), two patients (33.33%) had partial remission (PR), and one patient (16.67%) had progressive disease (PD). The overall survival rate was 66.67% (four out of six), and the mortality rate was 33.33%. The mean duration of follow-up was 2.5 months (range 1–13). One patient lost follow-up after three cycles, and three alive patients are currently on their second, fifth, and 13th cycles, respectively.

Discussion

JMML is a lethal clonal myeloproliferative disorder characterised by the uncontrolled proliferation of myeloid and monocytic cell lineages due to mutations in the RAS signalling pathways. The median age in our study was 4.5 years (range 1–9 years) with female predominance, which was comparable to the study done by Saha et al [7], where the median age was 5 years with the majority being female. However, study done by Subramanian et al [8] showed male predominance

in their JMML case series. Common clinical findings include symptoms and signs of anaemia, thrombocytopenia, and hepatosplenomegaly, as seen in our study, which was comparable to the studies done by Ghariani et al [9]. Ocular involvement as seen in case 1, is a rare finding in JMML, and only a few cases have been described in the literature regarding the same [10,11].

Although the median TLC count reported in a large cohort of patients was $33x1x10^9$/L (range $5\text{-}259x10^9$/L) [12], we found both TLC and absolute monocyte count on the higher side. Peripheral smear and bone marrow examination showed monocytosis, left shift, along with dysmyelopoeisis and dysmegakaryopoeisis, which was consistent with the literature [13]. Trisomy 8 was the most common cytogenetic abnormality seen in our study, which was comparable to the triology case series done by Azma et al [14]. Genetic study is of utmost importance in JMML, as wait and watch is the policy in the case of mutations in the CBL gene and a few cases of NRAS gene mutations. Although PTPN11 is the most common mutation seen in JMML (35% cases) [2], in the present study, out of four patients in whom genetic testing was successful, there were 50% cases with the NRAS mutation.

We used azacitidine (a DNAmethyltransferase-inhibiting azanucleoside assumed to reverse epigenetic dysregulation in malignant cells) as a frontline therapy in all the cases. Although the overall survival rate in JMML is poor, with 5-year survival rates being 50% even after allogenic HSCT [2], our results using azacitidine as a frontline therapy are promising, with an overall survival rate of 66.66%. Complete remission (CR) was observed in 50% of the cases, which was similar to the study done by Stenger et al [5] in which CR was observed in nine out of 18 patients (50%).

In conclusion, JMML is a rare, unique, and aggressive disease with clinical and hematological overlap with other myeloproliferative neoplasms. An accurate diagnosis is important for early treatment initiation. Azacitidine is an effective treatment option, especially in resource poor developing countries.

Declaration of patient consent

-The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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