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

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Abstract

**Background:** Juvenile myelomonocytic leukemia (JMML), previously known as juvenile chronic myeloid leukemia, is a rare, unique, and aggressive myeloproliferative neoplasm of early childhood. Making a diagnosis of JMML is challenging because of the overlapping clinical and haematological features with other myeloproliferative neoplasms (MPN). However, some unique features like monocytosis, the absence of BCR-ABL translocation, and the presence of specific mutations (PTPN-11, K-RAS, N-RAS, CBL, or NF1) clinch the correct diagnosis.

**Methods:** A prospective analysis of six JMML patients with variable clinical features treated with injection azacitidine as frontline therapy during the study period of 2 years. **Results:** The median age was 4.5 years with male:female ratio 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%) had progressive disease (PD). The overall survival rate was 66.67% (four out of six), and the mortality rate was 33.33%. **Conclusion:** Azacitidine is an effective treatment option as upfront therapy for JMML, especially in resource poor developing countries.

**Keywords:** JMML- Myeloproliferative neoplasm- Monocytosis- Mutation

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

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All diagnosed JMML patients were included in the study, and those who proceeded with hematopoietic stem cell transplant (H SCT) 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, of which two proceeded with H SCT and were excluded from the present study. Hence, a total of six patients were included in the present study.

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)/Sex</th>
<th>Presentation</th>
<th>Clinical findings</th>
<th>Laboratory findings</th>
<th>Chemotherapy</th>
<th>Outcome/ Follow up</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5/Female</td>
<td>Fever, Pallor, Orbital mas</td>
<td>Spleen 4 cm, Cervical LAP</td>
<td>TLC 78.72 x 10^9/l, Absolute monocyte count 16.45 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>1st cycle azacitidine</td>
<td>Dead</td>
<td>PD</td>
</tr>
<tr>
<td>2</td>
<td>8/Female</td>
<td>Pallor, Epistaxis</td>
<td>Liver 2 cm, Spleen 6 cm</td>
<td>TLC 54.56 x 10^9/l, Absolute monocyte count 9.92 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>2nd cycle vincristine + cytarabine + etoposide</td>
<td>Alive/ 2 months</td>
<td>PR</td>
</tr>
<tr>
<td>3</td>
<td>6/Male</td>
<td>Pallor, abdominal fullness</td>
<td>Liver 10 cm, Spleen 14 cm</td>
<td>TLC 39.92 x 10^9/l, Absolute monocyte count 7.32 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>2nd cycle azacitidine</td>
<td>Dead</td>
<td>CR</td>
</tr>
<tr>
<td>4</td>
<td>5/Female</td>
<td>Fever, Pallor</td>
<td>Liver 2 cm, Spleen 2 cm, Cervical LAP</td>
<td>TLC 124.56 x 10^9/l, Absolute monocyte count 24.47 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>1st cycle azacitidine</td>
<td>Alive</td>
<td>PR</td>
</tr>
<tr>
<td>5</td>
<td>1/Female</td>
<td>Pallor, Multiple petechial spots</td>
<td>Spleen 2 cm</td>
<td>TLC 61.24 x 10^9/l, Absolute monocyte count 12.34 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>13 cycles azacitidine/13 months</td>
<td>Alive</td>
<td>CR</td>
</tr>
<tr>
<td>6</td>
<td>4/Male</td>
<td>Fever, Pallor</td>
<td>Spleen 4 cm</td>
<td>TLC 28.77 x 10^9/l, Absolute monocyte count 4.56 x 10^9/l, Myeloid/erythroid precursors in PB</td>
<td>5 cycles azacitidine/5 months</td>
<td>Alive</td>
<td>CR</td>
</tr>
</tbody>
</table>

Table 1. JMML Patient Characteristics (n=6)
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 DNA methyltransferase-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.

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 5-259x10^9/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 dysmyelopoiesis and dysmegakaryopoiesis, which was consistent with the literature [13]. Trisomy 8 was the most common cytogenetic abnormality seen in our study, which was comparable to the trilogy 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.

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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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