# Juvenile myelomonocytic leukemia in a child: a case report of palliative chemotherapy and literature review applied to limited resources centers

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**Abstract**

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy in children with incidence 1.2 per million children per year. Hereby we present a case report and brief literature review of JMML in a child, especially focused on applicability in low-middle income countries. A 3.5 years-old male was referred to our tertiary center due to pallor, enlarging abdomen and neck mass, recurrent fever and chronic diarrhea. Initial laboratory workup showed Hb 6.4 g/dl, white blood cell 315.62 x 103/uL, and platelet 17 x 103/uL. Blood smears showed 10% suspected blast, 17% myelocyte, 17% metamyelocytes, with thrombocytopenic crisis. The HbF level was 5.8%. BCR-ABL gene was tested negative. The patient was diagnosed as juvenile myelomonocytic leukemia. Considering that HSCT was not able to be done in our center and lack of financial possibilities to seek that treatment abroad, family agreed to do palliative treatment. Patient was treated with 6-mercaptopurin and subcutaneous cytarabine. Four weeks after receiving 6-MP, white blood cell count decreased to 10,6 x 103/uL and spleen size was half of the original size. Patient continued the chemotherapy until week 15, chemotherapy was stopped, but 16 weeks after the diagnosis of JMLL, he developed severe thrombocytopenia, endophthalmitis, sepsis and passed away.

## INTRODUCTION

Juvenile myelomonocytic leukemia (JMML) is a rare hematopoietic malignancy in children with features characteristic of both myelodysplastic and myeloproliferative disorders.[1] In 2008, the World Health Organization (WHO) classified JMML into myelodysplastic syndrome (MDS) or myeloproliferative neoplasms (MPN).[2] This rare disease has incidence rate of 1.2 per million children per year or 1% of all childhood leukemias.[3] JMML is associated with two inherited diseases: neurofibromatosis type 1 (NF1) and Noonan syndrome.[1] JMML affects young children with median age at diagnosis was 20-24 months and has a significant male predominance (2.5:1).[4,5] Cytogenetic analysis of JMML patients showed monosomy 7 in 24-33% of patients, other chromosomal abnormalities in 10-27%, and normal karyotype in 40-60%.[5]

The symptoms of JMLL are fever and general malaise, plus symptoms due to infiltration of organs by malignant cells, infection, pallor, lymphadenopathy, marked hepatosplenomegaly, cutaneous lesions, and hemorrhagic manifestations. Hematologic abnormalities are caused by disruption of signal transduction in the RAS pathway.[6]Leukocytosis with monocytosis and myeloid/erythroid precursors, anemia, and thrombocytopenia are common findings in peripheral blood. The median blast cell percentage in peripheral blood is less than 2% and rarely exceeds 20%. Bone marrow abnormalities are non-specific and less informative than peripheral blood smear.[5] JMML patients respond poorly to chemotherapy and probability to survival without allogenic hematopoietic stem cell transplantation (HSCT) is less than 10% or 10-12 months after diagnosis.[5] Even after HSCT, 5-year event survival rate is only 44-53%.[7]Hereby we present a case report and brief literature review of JMML in a child, especially focused on applicability in low-middle income countries.

## CASE REPORT

A 3.5 years-old male was referred to our tertiary center due to pallor, enlarging abdomen and neck mass noticed for the last year. The mother also mentioned recurrent fever and diarrhea for the last two years. Patient's weight was 9.4 kg and height 76 cm. Physical examination showed anemia, breathing difficulty, enlarged unilateral neck lymph node with diameter of 3 cm, enlarged liver 7 cm below costal margin, splenomegaly Schuffner IV, and peripheral edema. He was diagnosed as tuberculosis and treated with triple therapy, probably this was a false diagnosis, JMML being the cause of his symptoms.

The initial routine blood test showed hemoglobin content of 6.4 g/dl, white blood cell counts of 315.62 x $10^3$/uL, neutrophils of 180.5 x $10^3$/uL, lymphocytes of 23.4 x $10^3$/uL, monocytes of 77.93 x $10^3$/uL, and platelets of 17 x $10^3$/uL. Blood smears showed normocytic anemia, hypercellularity with various stadia of cell maturation, i.e. 10% suspected blast, 17% myelocyte, 17% metamyelocytes, with thrombocytopenic crisis. The HbF level was 5.8%. BCR-ABL gene was tested negative. Chest x-ray and echocardiography were within normal limits. An abdominal ultrasound showed enlargement of liver, spleen, peripancreatic and paraaortic lymph nodes.

Our patient was diagnosed as juvenile myelomonocytic leukemia, accompanied by cachexia. Considering that HSCT was not able to be done in our center, lack of financial possibilities to seek that treatment abroad, and the complex condition of the patient, the family agreed to do palliative treatment with the aim to keep him in reasonably good clinical condition for as long as possible. Patient was treated with 6-mercaptopurin and subcutaneous cytarabine. The treatment plan consisted of 3 cycles of 4-weeks regimen, given the total of 12 weeks chemotherapy. 6-MP was given daily, started with dose of 10 mg/m$^2$/day and increased 20% every cycle, if tolerated, until maximum 20 mg/m$^2$/day. Subcutaneous cytarabine 10 mg/m$^2$ was given every week, except for the first day of every cycle. Chemotherapy was well-tolerated, and patient's general condition was improving, his weight increased to 10.2 kg. He survived a bout of COVID infection, with mild cough and a positive COVID antigen test. There was no fever, bleeding signs, nor breathing difficulty. Four weeks after receiving 6-MP, the white blood cell count decreased to 10,6 x $10^3$/uL and spleen size was half of the original size (categorized as complete clinical response). The 6-MP dose was increased 20% in the second cycle and also well-tolerated. Patient continued the chemotherapy at home until week 15, chemotherapy was stopped, but 16 weeks after the diagnosis of JMLL, he developed severe thrombocytopenia, endophthalmitis, sepsis and passed away.

## DISCUSSION

The presenting clinical picture of this patient with pallor, persistent fever, cervical lymphadenopathy, hepatosplenomegaly and hyperleukocytosis directed to hematological malignancy. The peripheral blood smear showed less than 20% blasts. The myeloblast predominance in blood smear suggested a diagnosis of the myeloid lineage. This patient was initially diagnosed as chronic myeloid leukemia, shortly treated with hydroxyurea, until further workups showed negative BCR-ABL gene and increased HbF. The diagnosis of JMML is based on diagnosis criteria per 2016 revision to World Health Organization Classification (Table 1).[8,9]

This patient fulfilled all of the items in Category 1 (peripheral blood monocyte count >1000/uL, blast in peripheral blood <20%, splenomegaly, absence of BRC-ABL gene) and two items in the Category 3 (circulating myeloid precursors and increased HbF for age). This patient also had the epidemiologic characteristics of JMML, i.e. male sex and age less than 6 years old. The pathogenesis of JMML involves disruption of signal transduction along the RAS pathway, with resultant selective hypersensitivity of JMML cells to GM-CSF. Unfortunately, we could not perform laboratory tests to find aberrations in the RAS pathway.

Marked splenomegaly and hepatomegaly are usually found and may cause abdominal discomfort and breathing difficulty. Lymphadenopathy is observed in about half of the patients and leukemic infiltrates may give rise to enlarged tonsils. Peribronchial and interstitial pulmonary infiltrates may be evident on chest x-ray and manifests as cough and respiratory distress. Central nervous system involvement is uncommon in JMML. Cutaneous involvement is frequent and most often appeared as eczematous eruptions or indurated raised

lesions with a central pale area.[10]

Allogenic hematopoietic stem cell transplantation (HSCT) is the only curative regimen for JMML. Currently, no therapy other than HSCT has been proven to result in long-term remission. HSCT can achieve long-term event-free survival in about 50% of patients, but it still has a high relapse rate at 30-40%.[11] In the absence of treatment, the progression of JMML is highly variable, including blast crisis, acute leukemia or even spontaneous partial or complete remission.[12]

Currently, there is no proven chemotherapy known to achieve complete remission for JMML.[13] AML protocols for intensive chemotherapy can induce temporary remission in JMML, but this approach is also very toxic. The European Working Group (EWOG-MDS) trial reported no significant difference in event-survival rate and mortality of AML-type chemotherapy compared to less intensive treatment.[11] For many decades, cytoreductive therapy with 6MP at a 50 mg/m2 dose or low dose i.v. cytarabine in a 40 mg/ $m^2$ dose for 5 days have been used to control the JMML symptoms before HSCT.[14] In aggressive cases, high dose fludarabine 30 mg/$m^2$ and cytarabine 2 g/$m^2$ daily for 5 consecutive days have been adopted by some centers.[15] JMML sometimes was sensitive to 6MP, and cytosine arabinoside (Ara-C) was added, because of its efficacy in AML. However, neither intensive nor low dose chemotherapy have been demonstrated to improve the outcome of patients with JMML.[13] Various combinations of busulfan (BU), melphalan (MRL), cyclophosphamide (CY) and fludarabine (FLU) have been tested as conditioning regimens.[13] Shakashita et al. found that BU/L-PAM/CY and BU/L-PAM/FLU combinations were associated with higher overall survival rate that total body irradiation or BU alone.[16] Due to unavailability of HSCT in our center, we opted for chemotherapy for controlling the disease. We used mercaptopurine and cytarabine due to its wide studies and availability in our center.

Jin Kang, et al. in Korea proposed a novel regimen for newly diagnosed JMML lacking access to transplantation. They proposed a standard regimen in 3-weeks interval consisting the combination of chemotherapy (Ara-C, etoposide, and vincristine) and differentiation therapy (isotretinoin). If disease relapsed or progressed, they continued to salvage regimen consisting of chemotherapy (Ara-C, etoposide) and differentiation therapy (low-dose Ara-C) in 3-4 weeks interval. This regimen was found to be safe and effective, but the study was only done in 5 JMML patients.[17] Another regimen was tested by Feng X et al. in China, consisting of decitabine, cytarabine, and fludarabine. They reported that this regimen is safe, effective, and feasible with a response rate of 97%. Although, the complete remission rate was low and mostly partial.[18] Given that DNA hypermethylation of certain genes is contributing to the aggressiveness of JMML, azacytidine (AZA), a DNA hypomethylating agent, has been tested as potential treatment for JMML. Cseh, et al. in their retrospective study treated 9 JMML patients with low-dose azacytidine prior to HSCT and highlighted two full remissions and two partial remissions. However, there were several adverse events (severe neutropenia, skin rash, and gastrointestinal problems).[19] Further study by Leoncini, et al. suggested that azacytidine is particularly beneficial in JMML patients with high methylation levels.[20]Fabri, et al. in Slovakia tested a novel approach using azacytidine 75 mg/m2 i.v. on days 1 to 7 of a 28-day cycle as a bridging therapy before HSCT and reported good response and favorable toxicity.[21]

Age, platelet count, and percentage of HbF at diagnosis are the main prognostic factors in JMML. Age >2 years at diagnosis, platelet count <33 x $10^6$/mm3, and HbF >10% are related to short survival.[5] The reasons as to why these factors portend a poor prognosis is still unknown. This patient had bad prognosis due to his age at diagnosis was older than 2 years old, initial low platelet count, and cachexia. In most patients, JMML is a rapidly progressive fatal disorder if untreated. The probability of survival without allogenic HSCT is less than 10%. Left untreated, JMML is fatal with 80% of patients surviving less than 3 years. Median survival rate is 0.9 – 1.4 years. Most untreated patients die from respiratory failure due to pulmonary infiltration with leukemic cells and progression to acute leukemia is observed in fewer than 20% of patients.[5]

In the setting of a terminal illness with limited available therapy, palliative care is an appropriate approach. Palliative care is a patient-centered approach that aim to improve the quality of life of patients and the family through prevention and relief of sufferings by means of early identification and treatment of pain and other physical, psychosocial, and spiritual problems.[22] Palliative care may or may not include the use

of cytostatic drugs to improve the clinical condition and to extend life, however thia approach has the risk of severe side effects too. Provision of palliative care for children is different from adults based on several reasons: (1) evaluation of pain severity and quality of life is difficult, (2) communication with children about disease, treatment, and death is under influence of their developmental stages.[23] The application of palliative care in cancer patients can decrease the number of unnecessary procedures, length of hospital stays, the need for intensive care, facilitate pain management, and improve communication among parents and health care team.[24]

Our patient had a history that suggested he was suffering from JMML already for about 2 years before he reached the Estella Clinic for Children with Cancer and Blood Diseases. He came from a small town about 400 km or 10 hours car drive away from Manado. After making the diagnosis of JMML, when he was in cachectic condition, he was treated with a simple palliative chemotherapy course, 6MP orally daily plus Cytarabine subcutaneously weekly. He improved greatly, both clinically and in laboratory values. After 2 months he came home with his family and had a good quality of life until in the end probably low WBC counts and low platelets led to his death 4 months after the start of palliative chemotherapy.

Unfortunately, access to pediatric palliative care in low- or middle-income countries is limited and mostly focused on adult patients. Lack of knowledge about the principle of palliative care and misperceptions about palliative care are the major barriers that limit the development of palliative service in low- and middle-income countries.[25] Therefore, providing education and training on clinicians working in pediatric oncology department is one of the initial steps necessary to develop palliative care for pediatric cancer patients.

## CONFLICT OF INTEREST

None declared.

## REFERENCES

1. Yoshimi A, Kojima S, Hirano N. Juvenile myelomonocytic leukemia: epidemiology, etiopathogenesis, diagnosis, and management considerations. Pediatr Drugs 2010;12:11-21.
2. Tefferi A, Vardiman JW. Classification and diagnosis of myeloproliferative neoplasms: the 2008 World Health Organization Criteria and point-of-care diagnostic algorithms. Leukemia 2008;22:14-22.
3. Chan RJ, Cooper T, Kratz CP, Weiss B, Loh ML. Juvenile myelomonocytic leukemia: a report from the 2nd international JMML symposium. Leuk Res 2009;33:355-62.
4. Yoshida N, Hirabayashi S, Watanabe S, et al. Prognosis of 75 patients with juvenile myelomonocytic leukemia: prospective study by MDS committee in the Japanese Society of Pediatric Hematology. Rinsho Ketshueki 2011;52:1853-8.
5. Niemeyer CM, Arico M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a retrospective analysis of 110 cases. European Working Group on Myelodysplastic Syndromes in Childhood (EWOG-MDS). Blood 1997;89:3534-43.
6. Sakashita K, Matsuda K, Koike K. Diagnosis and treatment of juvenile myelomonocytic leukemia. Pediatrics International 2016;58:681-90.
7. Yabe M, Ohtsuka Y, Watanabe K, Inagaki J, Yoshida N, Sakashita K, et al. Transplantation for juvenile myelomonocytic leukemia: a retrospective study of 30 children treated with a regimen of busulfan, fludarabine, and melphalan. Int J Hematol 2015;101:184–90.
8. Dvorak CC, Loh ML. Juvenile myelomonocytic leukemia: molecular pathogenesis informs current approaches to therapy and hematopoietic cell transplantation. Front Pediatr 2014;25.eCollection.
9. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Healt Organization classification of myeloid neoplasms and acute leukemia. Blood 2016;127:2391-2405.
10. Locatelli F, Algeri M, Merli P, Strocchio L. Novel approaches to diagnosis and treatment of juvenile myelomonocytic leukemia. Expert Rev Hematol 2018;11:129-43.
11. Locatelli F, Nolke P, Zecca M, Korthof E, Lanino E, Peters C, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-

MDS/EBMT trial. Blood 2005;105:410-19.
12. Honda Y, Tsuchida M, Zaike Y, Masunaga A, Yoshimi A, Kojima S, et al. Clinical characteristics of 15 children with juvenile myelomonocytic leukaemia who developed blast crisis: MDS Committee of Japanese Society of Paediatric Haematology/Oncology. Br J Haematol 2014;165:682–7.
13. Gupta DK, Meena JP, Chopra A, Tanwar P, Seth R. Juvenile myelomonocytic leukemia-a comprehensive review and recent advances in management. Am J Blood Res 2021;11:1-21.
14. Bergstraesser E, Hasle H, Rogge T, Fischer A, Zimmerman M, et al. Non-hematopoietic stem cell transplantation treatment of juvenile myelomonocytic leukemia: a retrospective analysis and definition of response criteria. Pediatr Blood Cancer 2007;49:629–33. https://doi. org/10.1002/pbc.21038.
15. Niemeyer CM, Kratz C. Juvenile myelomonocytic leukemia. Curr Oncol Rep 2003;5:510–15.
16. Sakashita K, Matsuda K, Koike K. Diagnosis and treatment of juvenile myelomonocytic leukemia. Pediatr Int 2016;58:681–90.
17. Jin Kang H, Young Sin H, Soo Choi H, Seop Ahn H. Novel regimen for the treatment of juvenile myelomonocytic leukemia (JMML). Leukemia Research 2004;28:167-70.
18. Feng X, Peng Z, He Y, Li C, Ruang Y, Liu X, et al. Improvement of survival in JMMLl by induction regimen of decitabine + cytarabine + fludarabine before hematopoietic stem cell transplantation: study of 33 cases in single center. Blood 2019;134(suppl):4267.
19. Cseh A, Niemeyer CM, Yoshimi A, Dworzak M, Hasle H, van den Heuvel-Eibrink MM, et al. Bridging to transplant with azacitidine in juvenile myelomonocytic leukemia: a retrospective analysis of the EWOG-MDS study group. Blood 2015;125:2311–3.
20. Leoncini PP, Vitullo P, Di Florio F, Tocco V, Cefalo MG, Pitisci A, et al. Whole Genome MBD-seq reveals different CpG methylation patterns in Azacytidine-treated juvenile myelomonocytic leukemia (JMML) patients. Br J Haematol 2018;182:909-12.
21. Fabri O, Horakova J, Bodova I, Svec P, LaluhovaStriezencova Z, et al. Diagnosis and treatment of juvenile myelo-monocytic leukemia in the Slovak Republic: novel approaches. Neoplasma 2019;66:818-24.
22. World Health Organization. Definitions of palliative care. Geneva; 2002; 2017.
23. Committee on Hospital Care and Institute for Patient-and Family-Centered Care. Patient-and-family centered care and the pediatrician's role. Pediatrics 2012;129: 394-404.
24. Feudtner C, Friebert S, Jewell J, Carter B, Hood M, Imaizumi S, et al. Pediatric palliative care and hospice care commitments, guidelines, and recommendations. Pediatrics 2013;132:966-72.
25. Doherty M, Thabet C. Development and implementation of a pediatric palliative care program in a developing country. Frontiers Pub Health 2018;6: doi: 10.3389/fpubh.2018.00106.

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