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Challenges in the Management of Juvenile Myelomonocytic Leukaemia in Hong Kong Over the Past Two Decades

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Abstract Juvenile myelomonocytic leukaemia (JMML) is a rare myeloid malignancy of childhood. The diagnosis and treatment of this disease still remain as major clinical challenges. We aim to describe the clinical and pathological findings, as well as treatment outcomes of eight patients with JMML who received treatment in two hospitals in Hong Kong between 1993 and 2011. One patient with Noonan syndrome showed spontaneous resolution of disease. Four patients underwent allogeneic haematopoietic stem cell transplantation during 1996 to 2007. Three of them died of post-transplant relapse and refractory disease or transplant-related toxicity. The surviving transplanted patient had chronic graft-versus-host disease for 4 years, and eventually showed evidence of disease relapse with documented mixed chimerism. The other three patients who received supportive treatment were alive with persistent disease. Our future works should focus on optimising therapy and improving treatment outcome for JMML patients.

Key words Case series; Diagnosis; Juvenile myelomonocytic leukaemia; Treatment outcome

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Introduction

Juvenile myelomonocytic leukaemia (JMML) is an aggressive clonal disorder of childhood. It accounts for 2-3% of all pediatric hematologic malignancies.[1,2] The World Health Organization Classification classifies JMML as a myelodysplastic/myeloproliferative neoplasms (MDS/MPN) in children.[3,4] This category currently encompasses most cases formerly diagnosed as juvenile chronic myeloid leukaemia (JCML), chronic myelomonocytic leukaemia (CMML) of infancy and infantile monosomy 7 syndrome. The median age at presentation is two years.[5,6] Typical presenting features include constitutional symptoms (e.g., malaise, pallor, and fever), organomegaly and a high circulating white blood cell (WBC) count with peripheral monocytosis and circulating myeloid precursor cells. These are non-specific findings that can be seen transiently in bacterial or viral infections in young children.[7-9] And sometime it may have to differentiate from myeloid leukaemia with low blast counts as well.[10] The diagnostic criteria of the International JMML Working Group have been widely adopted.[11] They include sophisticated

investigations such as cytogenetics and *in-vitro* culture. These are either non-specific or the special technique is not widely available. Based on the advances in understanding of the molecular pathogenesis of JMML involving the deregulation of the Ras/MAPK signaling pathway, alternative diagnostic criteria were proposed. These incorporate *NF1*, *RAS*, and *PTPN11* mutational status or presence of monosomy 7 into the diagnostic categories.[12]

Although the diagnosis of JMML has been refined, challenges continue to exist in therapy and prognostication. The probability of survival without allogeneic haematopoietic stem cell transplantation (HSCT) is less than 10%.[5] While the current standard of care is HSCT, the results of the most recent trials showed an event-free survival of only 50%, with an unacceptably high relapse rate.[13-15] In a few patients, clinical resolution and long-term survival was described in the absence of therapy.[5,16] Moreover, the correlation between mutational status and clinical outcome remains controversial. We present here the first case series of JMML patients treated in Hong Kong over the past two decades, and highlight the need for further studies to formulate an evidence-based treatment strategy to manage this disease which currently has a very dismal prognosis.

Methods

All paediatric JMML patients treated in Queen Mary Hospital (QMH) and Tuen Mun Hospital (TMH) between 1993 and 2011 were recruited from clinical databases. Socio-demographic, clinical and laboratory characteristics, treatment and outcome of the patients were collected from review of medical records. Accrued data were analyzed using descriptive statistics. The length of follow-up was calculated from the date of diagnosis until the last clinical information on the patient up to October 2011.

Results

Patient Demographics

We identified eight patients with a diagnosis of JMML treated in our two institutes over an 18-year period (1993-2011), with a median follow-up time of 24 months (range, 5 to 53 months). Table 1 shows their epidemiological and clinical and laboratory features at diagnosis. The median age at diagnosis was 2.3 years (range, 9 months to 11 years); with a male-to-female ratio of 3:1. Seven patients were Chinese and one was an Indonesian. Three patients (Patient 1, 4, and 5) presented first to QMH and TMH, while the remaining five were referred from other hospitals and had received prior treatment.

Clinical Features and Basic Laboratory Findings

Fever was the most common symptom, present in 75%, followed by bleeding (37%) and diarrhoea (37%). Salmonella sepsis was documented in one patient (Patient 3) at diagnosis. One patient (Patient 7) presented with coexistent cytomegalovirus (CMV) infection. The median presenting WBC and absolute monocyte count were $23.6x10^9$/L (range, 12.5 to $89.1x10^9$/L) and $4.6x10^9$/L (range, 0.9 to $10.7x10^9$/L), respectively. The median haemoglobin concentration was 10.4 g/L (range, 8.3 to 11.5 g/dL). The median platelet count was $77x10^9$/L (range, 30 to $145x10^9$/L). As shown in Figure 1, peripheral blood smear of patients typically demonstrated leukocytosis and monocytosis with a leucoerythroblastic blood picture. Hypercellularity with active granulopoiesis were noted in all marrow specimens. Mild to moderate degree of dysplastic features were also found in marrow cells in three patients. The median blast count in peripheral blood and bone marrow was 6% (range, 3 to 24%) and 5% (range, 2 to 18%), respectively. Three of eight patients presented with an elevated fetal haemoglobin (HbF) level for age.

Genetic Study Results

Cytogenetic analysis demonstrated monosomy 7 in three patients. Multiple monosomies were seen in one patient. Addition of chromosomal material at 8q24.3 was found in two patients. Two patients had underlying neurofibromatosis type 1 (NF1) with a strong family history. One patient had Noonan syndrome (NS) with identified mutation in *PTPN11*, whereas another patient had *PTPN11* mutation detected at diagnosis of JMML with undetected clinical phenotypes of NS. *In-vitro* hypersensitivity to granulocyte-macrophage colony stimulating factor (GM-CSF) was observed in one patient where it was examined. Overall, all patients were compatible with diagnosis of JMML based on current WHO criteria[17] and the updated diagnostic criteria.[12]

Treatment and Outcome

Patients received different types of therapy, ranging from supportive care to intensive chemotherapy. Patient 6 received 13-*cis* retinoic acid therapy only. Treatment with intensive chemotherapy resulted in transient clinical improvements in Patient 2 and 8, who presented with

Table 1 Clinical characteristics and treatment prior to referral and diagnostic assessment of the eight paediatric patients with JMML

Clinical characteristics	Patient No.							
	1*	**2**	**3**	**4***	**5***	**6**	**7**	**8**
Ethnicity/Gender	Chinese/M	Chinese/M	Chinese/F	Chinese/M	Chinese/M	Chinese/M	Chinese/M	Indonesian/F
Age at presentation	2.5 years	10 years	1.5 years	3 months	1 month	1.5 years	3 months	8 years
Presenting features	Fever, bruises	Pallor	Fever, bruises	Fever, abdominal distension	Noonan syndrome, pallor, bleeding	Fever, diarrhoea	Fever, diarrhoea	Diarrhoea
Diagnosis prior to referral	–	CMML	JMML	–	–	MDS	CMV infection, JMML	JMML
Treatment prior to referral	–	HU, Ara-C	Supportive	–	–	13-cis retinoic acid	Supportive	VP-16, Ara-C
Age at referral	–	11 years	6 years	–	–	1.5 years	9 months	8 years
Category 1 (All of the following)**								
Splenomegaly***	√	√	√	√	√	√	√	√
Absence of *BCR/ABL1* fusion gene	√	√	√	√	√	√	√	√
Circulating monocytes >1 x10^9/L	√	√	√	√	√	√	√	√
Blasts in bone marrow <20%	√	√	√	√	√	√	√	√
Category 2 (At least one of the following)***								
Somatic mutation in *RAS* or *PTPN11*	N/A	N/A	√	N/A	√	N/A	N/A	N/A
Clinical diagnosis of NF1 or *NF1* gene mutation	N/A	N/A	N/A	√	N/A	N/A	N/A	√
Monosomy 7	X	√	X	X	X	√	X	√
Category 3 (Two of the following, if no category 2 criteria are met)**								
WBC >10x10^9/L	√	√	√	√	√	√	√	√
Circulating myeloid precursors	√	√	√	√	√	√	√	√
Increased HbF for age	√	X	√	√	X	X	X	X
Clonal cytogenetic abnormality (excluding monosomy 7)***	√	X	√	X	√	X	X	X
GM-CSF hypersensitivity	N/A	N/A	N/A	N/A	N/A	N/A	√	N/A

* Patient No.1, 4, and 5 were primarily diagnosed and treated in Queen Mary Hospital and Tuen Mun Hospital; **Current WHO criteria[17]; ***Proposed additions to the WHO criteria (Chan et al, 2009).[12]

√= presence; X = absence; N/A = not applicable.

Ara-C, cytarabine arabinoside; CMML, chronic myelomonocytic leukaemia; HbF, fetal haemoglobin; GM-CSF, granulocyte-macrophage colony-stimulating factor; HU, hydroxyurea; JMML, juvenile myelomonocytic leukaemia; MDS, myelodysplastic; CMV, cytomegalovirus; NF1, neurofibromatosis type 1; No., number; VP-16, etoposide; WBC, white blood cell count.

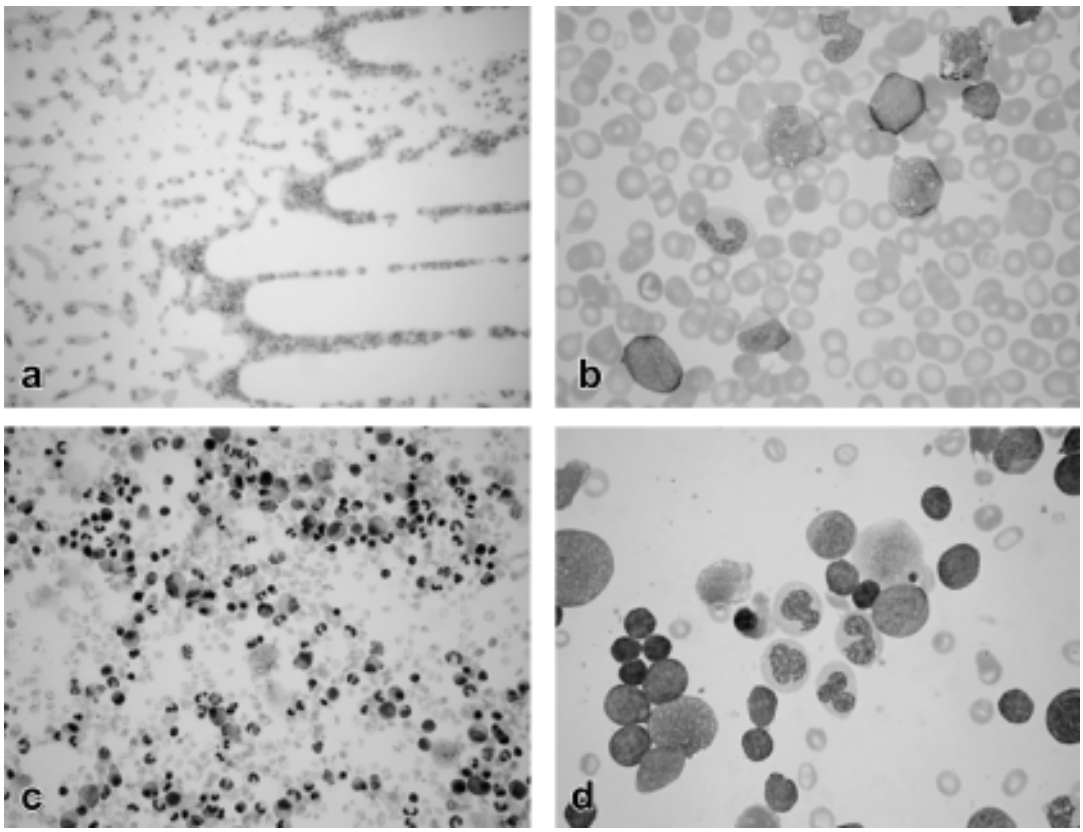

Figure 1 (a) Peripheral blood smear of Patient 4 showing marked leukocytosis (Wright stain, X 100). (b) Peripheral blood smear of Patient 4 showing monocytosis and presence of blasts (Wright stain, X 400). (c) Bone marrow smear of Patient 7 showing hypercellularity (Wright stain, X 100). (d) Bone marrow smear of Patient 4 showing dysgranulopoiesis and slight prominence of blasts (Wright stain, X 400).

hyperleukocytosis with excess blasts in peripheral blood. Complete remission could not be induced in any of those receiving chemotherapy.

Four of eight patients (Patient 1 to 4) underwent allogeneic HSCT during 1996 to 2007. Regarding the other four non-transplant patients, they were treated with supportive treatment while watchful waiting for appropriate donor identification. The median time from first admission in QMH to the first HSCT was 5.8 months (range, 5-8 months). Splenectomy/splenic irradiation before transplantation was performed in all patients, either prior to the first or second HSCT. Only Patient 1 received an HLA identical sibling transplant. Patient 2, 3, and 4 were recipients of HLA mismatched (for 1 to 2 out of 6 HLA antigens) related or unrelated transplants. Patient 1 had haematological relapse at 2 months after peripheral blood stem cell transplantation (PBSCT). A second HSCT was performed using bone marrow stem cells from the same donor. Subsequently, he died of disease progression at 3 months post-second HSCT. Patient 3 relapsed at eleven months after the first HSCT. She received donor lymphocyte infusions (DLI). However, she expired from disease progression at 3 months after DLI. Patient 2 developed primary engraftment failure, and subsequently received a second transplant with half-brother donor. Unfortunately, the disease was complicated with secondary acute respiratory distress syndrome immediately after stem cell infusion and he succumbed one week later to septicaemia. These three patients died of refractory disease or transplant-related toxicity at a median of 24 months after first diagnosis (range, 13 to 77 months). Patients 4 had refractory chronic graft-versus-host disease (cGVHD) of oral cavity and gastrointestinal tract 4 years after engraftment. Recently, he developed autoimmune haemolytic anaemia, raised WBC with monocytosis. Genetic monitoring showed a stable mixed chimerism

(approximately 30% donor cells). His cGVHD status and other clinical conditions remained stable while receiving supportive treatment. In the four patients (Patient 5 to 8) who did not receive HSCT, one patient (Patient 5) with NS, who presented with a JMML-like MPN in the infantile period, had spontaneously resolution of haematological abnormalities at 5 years of age. The other three non-transplant patients were alive with disease. The treatment and outcome of this patient cohort are summarised in Table 2.

Discussion

Unlike commonly seen in other myeloid malignancies of childhood, JMML is a rare mixed MDS/MPN of young children with a high mortality rate. The estimated incidence of childhood MDS among Chinese children was estimated to be 2.1/million children/year and JMML accounts for around half of the childhood MDS.[18] A local review of 21 JMML cases reported in the recent two decades (1993-

Table 2 Treatment and outcome of the eight paediatric patients with JMML at referral centre

Clinical	**Patient No.**							
characteristics	**1***	**2**	**3**	**4***	**5***	**6**	**7**	**8**
Interval between presentation and diagnosis	–	3 months	4.5 years	–	–	1 month	6 months	3 months
Interval between diagnosis and first HSCT	5 months	8 months	5 months	5 months	–	–	–	–
Treatment								
Treatment prior to first HSCT	Supportive	HU, Ara-C	Splenectomy	Splenectomy	Supportive	Supportive	Supportive	Supportive
First HSCT								
Type	MRD PBSCT	MMUD UCBT	MMUD PBSCT	MMUD UCBT	–	–	–	–
Response	Relapse	Graft failure	Relapse	Mixed chimerism	–	–	–	–
Treatment prior to second HSCT	Splenectomy	Splenic irradiation	–	–	–	–	–	–
Second HSCT								
Type	MRD BMSCT	MMRD PBSCT	–	–	–	–	–	–
Response	Relapse	2°ARDS						
Further treatment	–	–	2 x DLI	–	–	–	–	–
Response	–	–	Mixed chimerism	–	–	–	–	–
Outcome	Died of disease progression at 24 months after diagnosis	Died of infection at 13 months after diagnosis	Died of disease progression at 77 months after diagnosis	Alive with disease at 61 months after diagnosis	Alive with spontaneous disease remission at 48 months after diagnosis	Alive with disease at 31 months after diagnosis	Alive with disease at 13 months after diagnosis	Alive with disease at 7 months after diagnosis

* Patient No.1, 4 and 5 were primarily diagnosed and treated in Queen Mary Hospital and Tuen Mun Hospital.

Ara-C, cytarabine arabinoside; BMSCT, bone marrow stem cell transplantation; cGVHD, chronic graft-versus-host disease; CMML, chronic myelomonocytic leukaemia; DLI, donor lymphocyte infusion; HSCT, haematopoietic stem cell transplantation; HU, hydroxyurea; JCML, juvenile chronic myeloid leukaemia; JMML, juvenile myelomonocytic leukaemia; MMRD, mismatched-related donor (i.e., 4 to 5/6 HLA antigen-matched); MMUD, mismatched-unrelated donor (i.e., 4 to 5/6 HLA antigen-matched); MRD, match-related donor; NF1, neurofibromatosis type1; No., number; PBSCT, peripheral blood stem cell transplantation; UCBT, umbilical cord blood stem cell transplantation.

2010) does support the rarity of this disease in Hong Kong (Chan GCF, unpublished data). JMML usually manifests with nonspecific symptoms that are common to infectious diseases and other haematologic malignancies. JMML is known to mimic viral infections, including CMV, Epstein-Barr virus (EBV), human herpesvirus (HHV)-6, and parvovirus B19 infection.[19-24] Hypersensitivity to GM-CSF, which is a hallmark of JMML, has also been reported in isolated cases of CMV and HHV-6 infection.[21,23] Two patients from our case series, however, presented with concomitant JMML and infection. Combination of microbiological and histopathological investigations is extremely important for differential diagnosis. Absence of significantly elevated HbF and dysplastic features in marrow cells may also help to differentiate benign from malignant diseases.

The discovery of somatic and germ-line mutations encoding proteins in the Ras/MAPK signaling pathway have improved the diagnostic specificity for JMML. The recent proposed diagnostic criteria suggest combining genetic and morphological findings for diagnosis of JMML.[12] However, molecular diagnostic tools are still not routinely available. Only two patients from our series had been studied for *PTPN11* mutation, which is known to be mainly associated with NS.[25] In non-NS patients with JMML, *PTPN11* somatic missense mutations still represent the most frequent group of molecular lesions.[26] Patient 3 in this series carried a constitutional *PTPN11* 215C>T (Ala72Val) mutation which has been previously documented in de novo, non-syndromic JMML.[27-29] This patient presented at age of 1.5 years with fever, bleeding and hepatosplenomegaly. She received supportive treatment before proceeding to a mismatched related donor HSCT at 6 years of age because of disease progression. Eventually, she died of disease relapse at 15 months after HSCT. Another patient (Patient 5) was diagnosed with NS in infantile period. The diagnosis was based on clinical characteristics, including typical facial features, pectus carinatum, a height below the third percentile for age and cryptorchidism.[30,31] A known NS-associated *PTPN11* (218C>T, Thr73Ile) mutation was identified, which commonly predisposes to self-resolving JMML.[27-29] He also developed JMML at 2 years of age. Cytogenetic study of marrow cells showed an acquired abnormality of 8q [46, XY,add(8)(q24.3)]. Spontaneous remission occurred at 5 years of age. A recent marrow study in early 2011 showed granulocytic hyperplasia only, with a normal karyotype. These contrasting clinical courses in our two *PTPN11*-mutated patients suggest that the background of a *PTPN11* mutation (NS or non-NS) and/or its nature (specific amino acid substitution) may affect disease outcome and thus rational treatment in individuals. In non-NS patients, a phenomenon of 'self-resolving' JMML has been reported in patients with various homozygous *CBL* mutations and *RAS* mutations.[32-34] However, the exact prognostic significance of common specific mutations in JMML (*NF1*, *RAS*, *PTPN11, CBL*) remains to be elucidated in a large population. Collaborative studies of comprehensive genetic analysis in JMML are required to shed light on potential risk-adapted and advance targeted therapeutic interventions.

To formulate the treatment approaches in JMML is always challenging, especially in the absence of tractable molecular markers. According to dismal outcome for non-transplant approaches in the previous decade,[5] we proceeded to HSCT for patients who had been identified those HLA-compatible donors in the period of 1996-2007. Pre-transplant splenectomy was performed in our selected patients. The conditioning regimen published by the EWOG-MDS[35] was applied, which consists of busulfan, cyclophosphamide, melphalan for first transplants, and addition of total body irradiation (TBI) for second transplants. However, these previous transplant approaches are currently uncertain in terms of efficacy and impact on ultimate outcome. The second HSCT and DLI which was shown to facilitate disease remission in several studies[35-39] could not restore complete remission in our patients. This study illustrates that relapse is the major cause of treatment failure in JMML patients undergoing HSCT, and disease progression is the most frequent cause of death. Only one transplant survivor who has been suffering from protracted cGVHD, also suggests the importance of a graft-versus-leukaemia (GVL). This creates a management dilemma because aggressive immunosuppressive therapy may abolish the GVL effect, resulting in relapse. To control GVHD while maintaining GVL is critically essential for a durable remission. Advance transplant strategies, including the generation of GVL effect in JMML by reduced-intensity conditioning, inhibitory killer cell immunoglobulin-like receptor (KIR) ligand incompatibility[40-42] are being thoroughly investigated.

Conclusion

JMML is a hybrid MDS/MPN of early childhood. Although advances have been made in its pathogenesis, JMML remains as one of the most difficult paediatric myeloid malignancies to treat. Widely accessible genetic

analysis may facilitate diagnosis and provide further insights into genotype-phenotype correlation and prognostication of JMML. Studies to improve treatment outcome, in particular to minimise relapse rate, are urgently needed. International collaboration will be necessary to manage this rare but challenging disease.

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References

1. Aricò M, Biondi A, Pui CH. Juvenile myelomonocytic leukemia. Blood 1997;90:479-88.
2. Hasle H, Kerndrup G, Jacobsen BB. Childhood myelodysplastic syndrome in Denmark: incidence and predisposing conditions. Leukemia 1995;9:1569-72.
3. Vardiman J, Pierre R, Imbert M, et al. Juvenile yelomonocytic leukemia. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. Pathology and genetics of tumours of haematopoietic and lympoid tissues: World Health Organization classification of tumours. Lyon: IARC Press, 2001:55-7.
4. Hasle H, Niemeyer CM, Chessells JM, et al. A pediatric approach to the WHO classification of myelodysplastic and myeloproliferative diseases. Leukemia 2003;17:277-82.
5. Niemeyer CM, Aricò M, Basso G, et al. Chronic myelomonocytic leukemia in childhood: a report of 110 cases. Blood 1997;89: 3534-43.
6. Castro-Malaspina H, Schaison G, Passe S, et al. Subacute and chronic myelomonocytic leukemia in children (juvenile CML). Clinical and hematologic observations, and identification of prognostic factors. Cancer 1984;54:675-86.
7. Kirby MA, Weitzman S, Freedman MH. Juvenile chronic myelogenous leukemia: differentiation from infantile cytomegalovirus infection. J Pediatr Hematol Oncol 1990;12: 292-6.
8. Lorenzana A, Lyons H, Sawaf H, Higgins M, Carrigan D, Emanuel PD. Human herpes virus 6 infection mimicking juvenile myelomonocytic leukemia in an infant. J Pediatr Hematol Oncol 2002;24:136-41.
9. Manabe A, Yoshimasu T, Ebihara Y, et al. Viral infections in juvenile myelomonocytic leucemia: prevalence and clinical implications. J Pediatr Hematol Oncol 2004;26:636-41.
10. Chan GCF, Wang WC, Raimondi SC, et al. Myelodysplastic syndrome in children: Differentiation from acute myeloid leukemia with a low blast count. Leukemia 1997;11:206-11.
11. Pinkel D. Differentiating juvenile myelomonocytic leukemia from infectious disease. Blood 1989;91:365-7.
12. 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.
13. Locatelli F, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood 2005;105:410-9.
14. Manabe A, Okamura J, Yumura-Yagi K, et al. Allogeneic hematopoietic stem cell transplantation for 27 children with juvenile myelomonocytic leukemia diagnosed based on the criteria of the International JMML Working Group. Leukemia 2002;16: 645-9
15. Smith FO, King R, Nelson G, et al. Unrelated donor bone marrow transplantation for children with juvenile myelomonocytic leukaemia. Br J Haematol 2002;116:716-24.
16. Matsuda K, Shimada A, Yoshida N, et al. Spontaneous improvement of hematologic abnormalities in patients having juvenile myelomonocytic leukemia with specific RAS mutations. Blood 2007;109:5477-80.
17. Baumann I, Bennett JM, Niemeyer CM, et al. Juvenile myelomonocytic leukemia. In: Swerdlow SH, Campo E, Harris NL, Jaffe ES, Pileri SA, Stein H, Thiele J, Vardiman JW, editors. World Health Organization classification of tumours of haematopoietic and lympoid tissues. Lyon: IARC Press, 2008: 82-4.
18. Chan GCF. Experience on MDS and JMML from China / Hong Kong. In Lopes LF, Hasle H, editors. Myelodysplatic and Myeloproliferative Disorders in Children. Sao Paulo: Lemar Livraria, Editora Marina and Tecmedd Editora, 2003:271-6.
19. Kirby MA, Weitzman S, Freedman MH. Juvenile chronic myelogenous leukemia: Differentiation from infantile cytomegalovirus infection. Am J Pediatr Hematol Oncol 1990; 12:292-6.
20. Toyoda H, Ido M, Hori H, et al. A case of juvenile myelomonocytic leukemia with concomitant cytomegalovirus infection. J Pediatr Hematol Oncol 2004;26:606-8.
21. Moritake H, Ikeda T, Manabe A, Kamimura S, Nunoi H. Cytomegalovirus infection mimicking juvenile myelomonocytic leukemia showing hypersensitivity to granulocyte-macrophage colony stimulating factor. Pediatr Blood Cancer 2009;53: 1324-6.
22. Herrod HG, Dow LW, Sullivan JL. Persistent Epstein-barr virus infection mimicking juvenile chronic myelogeneous leukemia: Immunologic and hematologic studies. Blood 1983;61:1098-104.
23. Lorenzana A, Lyons H, Sawaf H, Higgins M, Carrigan D, Emanuel PD. Human herpesvirus-6 infection mimicking juvenile myelomonocytic leukemia in an infant. J Pediatr Hematol Oncol 2002;24:136-41.
24. Yetgin S, Cetin M, Yenicesu I, Ozaltin F, Uckan D. Acute parvovirus B19 infection mimicking juvenile myelomonocytic leukemia. Eur J Haematol 2000;65:276-8.
25. Tartaglia M, Mehler EL, Goldberg R, et al. Mutations in *PTPN11*, encoding the protein tyrosine phosphatase SHP-2, cause Noonan syndrome. Nat Genet 2001;29:465-8.
26. Tartaglia M, Niemeyer CM, Fragale A, et al. Somatic *PTPN11* mutations in juvenile myelomonocytic leukemia, myelodysplastic syndromes and acute myeloid leukemia. Nat Genet 2003; 34: 148-50.
27. Tartaglia M, Martinelli S, Cazzaniga G, et al. Genetic evidence for lineage-related and differentiation stage-related contribution of somatic PTPN11 mutations to leukemogenesis in childhood acute leukemia. Blood 2004;104:307-13.

28. Loh ML, Vattikuti S, Schubbert S, et al. Mutations in PTPN11 implicate the SHP-2 phosphatase in leukemogenesis. Blood 2004; 103:2325-31.
29. Kratz CP, Niemeyer CM, Castleberry RP, et al. The mutational spectrum of PTPN11 in juvenile myelomonocytic leukemia and Noonan syndrome/myeloproliferative disease. Blood 2005;106: 2183-5.
30. van der Burgt I. Noonan syndrome. Orphanet J Rare Dis 2007; 2:4.
31. Leung SSF, Tse LY, Wong GWK, et al. Standarts for anthropometric assessment of nutritional status of Hong Kong children. HK J Paediatr 1995;12:5-15.
32. Matsuda K, Shimada A, Yoshida N, et al. Spontaneous improvement of hematologic abnormalities of patients having juvenile myelomonocytic leukemia with specific *RAS* mutations. Blood 2007;109:5477-80.
33. Flotho C, Kratz CP, Bergstrasser E, et al. Genotype-phenotype correlation in cases of juvenile myelomonocytic leukemia with clonal *RAS* mutations. Blood 2008;111:966-7; author reply 967-8.
34. Loh ML, Sakai DS, Flotho C, et al. Mutations in CBL occur frequently in juvenile myelomonocytic leukemia. Blood 2009; 114:1859-63.
35. Locatelli F, Nollke P, Zecca M, et al. Hematopoietic stem cell transplantation (HSCT) in children with juvenile myelomonocytic leukemia (JMML): results of the EWOG-MDS/EBMT trial. Blood 2005;105:410-9.
36. Manabe A, Okamura J, Yumura-Yagi K, et al. Allogeneic hematopoietic stem cell transplantation for 27 children with juvenile myelomonocytic leukemia diagnosed based on the criteria of the International JMML Working Group. Leukemia 2002;16:645-9.
37. Yoshimi A, Niemeyer CM, Bohmer V, et al. Chimaerism analyses and subsequent immunological intervention after stem cell transplantation in patients with juvenile myelomonocytic leukaemia. Br J Hematol 2005;129:542-9.
38. Yoshimi A, Bader P, Matthes-Martin S, et al. Donor leukocyte infusion after hematopoietic stem cell transplantation in patients with juvenile myelomonocytic leukemia. Leukemia 2005;19: 971-7.
39. Yoshimi A, Mohamed M, Bierings M, et al. Second allogeneic hematopoietic stem cell transplantation (HSCT) results in outcome similar to that of first HSCT for patients with juvenile myelomonocyticleukemia. Leukemia 2007;21:556-60.
40. Koyama M, Nakano T, Takeshita Y, et al. Successful treatment of JMML with related bone marrow transplantation after reduced-intensity conditioning. Bone Marrow Transplant 2005;36:453-4.
41. Stachel DK, Leipold A, Kuhlen M, et al. Simultaneous control of third-degree graft-versus-host disease and prevention of recurrence of juvenile myelomonocytic leukemia (JMML) with 6-mercaptopurine following fulminant JMML relapse early after KIR-mismatched bone marrow transplantation. J Pediatr Hematol Oncol. 2005;27:672-4.
42. Lang P, Pfeiffer M, Teltschik H, et al. Natural killer cell activity influences outcome after T cell depleted stem cell transplantation from matched unrelated and haploidentical donors. Best Pract Res Clin Haematol 2011;24:403-11.