

# Myelo-Proliferative Disorders in Children: A Ten-Year-Experience of Single Institute in Baghdad, Iraq

Mazin F. Al-Jadiry<sup>1</sup>, Hasanein H. Ghali<sup>1</sup>, Salam B. Sultan<sup>2</sup>, Safa A. Faraj<sup>3\*</sup> and Salma A. Al-Hadad<sup>1</sup>

<sup>1</sup>Department of Pediatrics, College of Medicine, University of Baghdad, Children Welfare Teaching Hospital, Medical City, Baghdad, Iraq; <sup>2</sup>Ibn Al-Baladi Maternity and Children's Hospital, Baghdad, Iraq; <sup>3</sup>Department of Pediatrics, College of Medicine, Wasit University, Children Welfare Teaching Hospital, Medical City, Kut, Iraq

## Corresponding author:

Safa A. Faraj,  
Department of Pediatrics,  
College of Medicine,  
Wasit University,  
Children Welfare Teaching Hospital,  
Medical City, Kut, Iraq,  
Tel: +919423119433;  
E-mail: safaafaraj@uowasit.edu.iq

## Abstract

**Background:** The myelodysplastic syndromes (MDS) and myeloproliferative disorders (MPD) are rare in childhood, accounting for about 3% of childhood malignancies. It is helpful to consider these syndromes as part of a continuum with the myelodysplastic syndromes on one end and the myeloproliferative syndromes on the other, with a group of "bridging" syndromes in between. **Aim of the study:** To study the epidemiological and clinical features of Myeloproliferative disorders in Children Welfare Teaching Hospital (CWTH), Medical City, Baghdad. **Patients and Methods:** A retrospective study was done over 10-year period, between January 1, 2000 and December 31, 2009. Fifty consecutive pediatric patients below the age of 14 years with newly diagnosed MPS treated and followed at the oncology unit of CWTH were studied. A review study was done for these patients, including all available medical records including laboratory data. The diagnosis of MPD was suggested by bone marrow aspirate and/or peripheral blood film. WHO morphological classification was carried out in most of the patients. **Results and Discussion:** The analyzed group represents about 3.7% of all leukemias treated in the hospital during the study period. There were 31 patients met the criteria of chronic myeloid leukemia (CML), 15 with Juvenile Myelomonocytic Leukemia (JMM) and 4 with MDS. Male to female ratio of 1.2:1, 1.5:1 for CML & JMML respectively while in MDS all were males. Five (10%) patients refused any sort of treatment, nine patients (18%) were referred to other centers (2 for palliative treatment, 5 to receive treatment from their governorates as recommended by MOH and other two patients went abroad for Bone Marrow Transplant), 17 (34%) patients lost follow up, 15 (30%) patients died and 4 (8%) are alive in remission on treatment. **Conclusion:** High percentage of accelerated and blastic crisis of CML might reflect delay in diagnosis or aggressive behavior of the disease.

**Keywords:** Chronic myeloid leukemia; Myelodysplastic disorders; Iraq

## Introduction

Myeloproliferative disorders (MPD) are a group of clonal hematopoietic stem cell disorders characterized by aberrant proliferation of one or more myeloid lineages often with increased immature cells in the peripheral blood (PB). The 2008 World Health Organization Classification (WHO) of Tumors of Haematopoietic and Lymphoid Tissues defines myeloproliferative neoplasms as a phenotypically diverse group of clonal hematopoietic stem cell disorders characterized by (1) hyperproliferation of one or more of the components of the myeloid compartment and (2) evidence of increased immature cellular forms in the PB.<sup>[1]</sup> Chronic Myeloid Leukemia (CML); a myeloproliferative disease of stem cell origin, is characterized by the presence of the Philadelphia (Ph) chromosome and the bcr-abl oncogene.<sup>[2]</sup> Juvenile Myelomonocytic Leukemia (JMML) is a rare, clonal hematopoietic disorder of early childhood, characterized by proliferation of monocytic and granulocytic cells, along with myelodysplastic features.<sup>[3,4]</sup> The Myelodysplastic Syndrome (MDS) represents a heterogeneous group of disorders of hemopoiesis leading to variable degree of pancytopenia and often Acute Myeloid Leukemia.<sup>[5]</sup> A clear

understanding of the pathogenesis has been, and continues to be, elusive. In addition to the t(5;12) translocation discussed above, activating point mutations in the RAS oncogene appear to occur more frequently in CMML than in other diseases in the MDS and MPD categories, but again, these RAS gene mutations are not specific for a diagnosis of CMML.<sup>[2]</sup> Neither intensive nor moderate chemotherapy has been demonstrated to consistently improve the outcome of JMML children.<sup>[4]</sup>

The current study was done to study the epidemiologic, clinical profile, and outcome of myeloproliferative disorders in Children Welfare Teaching Hospital (CWTH), Medical City, Baghdad.

## Patients and Methods

A retrospective analysis of the data of 50 pediatric patients below

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 License, which allows others to remix, tweak, and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

**How to Cite this Article:** Al-Jadiry MF, et al. Myelo-Proliferative Disorders in Children: A Ten-Year-Experience of Single Institute in Baghdad, Iraq. *Ann Med Health Sci Res.* 2019;9:494-498

the age of 14 years with MPD; being diagnosed, treated and followed in CWTH, Medical City, Baghdad in the period from January 1st, 2000 to December 31st, 2009. An extensive review chart was accomplished for the whole study group, including all the available medical records and laboratory data. All the patients were followed till March 1st, 2012. The diagnosis of MPD was suggested by bone marrow (BM) aspirate and/or PB due to lack of cytogenetic studies and immunophenotyping during the period 2000-2009. According to morphological classification of WHO system, chronic phase of CML (CML-CP) was diagnosed by clinical presentation plus leukocytosis with shift to left with sequential orderly maturation of myeloid series in all stages with BM blasts of less than 10%. Accelerated phase (CML-AP) was defined by finding Blasts 10%-19% of PB White Cells or BM cells.<sup>[6]</sup> Blast crisis (CML - BC) presents as overt Acute Leukemia and is defined by more than or equal to 20% BM blasts or extramedullary blast proliferation.<sup>[7]</sup> Juvenile Myelomonocytic Leukemia (JMML) was diagnosed if by suggested clinical features as well as PB Monocyte count greater than  $1 \times 10^9/L$ , with blasts less than 20% of BM.<sup>[8]</sup> Myelodysplastic Syndrome (MDS) was diagnosed by clinical features as well as laboratory finding like sustained unexplained cytopenia (neutropenia, thrombocytopenia, or anemia), or bi-lineage morphologic myelodysplasia and blasts (1-19%) in the BM.<sup>[9]</sup> Different treatment options were adopted according to mode of presentation and the available chemotherapy medications. Chronic phase patients were treated with Busulphan, hydroxyurea, or/and Imatinib. Lymphoblastic crises were treated with protocol modified from MRC UKALL 1997 and 2003.<sup>[10]</sup> Myeloblastic crises were treated with regimen modified from Medical Research Council, United Kingdom, MRC-AML 12 trial.<sup>[11]</sup> For MDS or JMML; supportive treatment was the available option. When the remission state attained, (Blast in BM less than 5%), treatment of chronic phase

was resumed. Patient data were tabulated and processed using SPSS (Statistical Package for the Social Sciences 13.0) for windows.<sup>[12]</sup>

## Results

The retrospective analysis identified 50 pediatric patients who were 14 years or younger and met the diagnosis of MPD. An average of 5 newly diagnosed children were admitted to Oncology unit in CWTH every year during the period 2000-2009, this represented about 3.7% of all leukemia (1354) seen in children. Twenty patients (40%) were from Baghdad, while the other 30 patients were from different governorates. There were 31 patients met the criteria of CML, 15 with JMML and 4 with MDS as seen in Table 1. Among CML cases, 22 (44%) patients were in CML-CP, 6 (12%) CML-AP and in 3 (6%) CML-BC; of whom 2 with lymphoid crisis and 1 with myeloid crisis. Out of the JMML cases, 4 of them (8%) presented with blastic crisis.

Demographic and clinical data are presented in Table 2; the median age was 9.1 years (5 months -13.8 years) for CML, 3 years (4 months -13.9 years) for JMML, and 6.9 years (range 22 months -14.5 years) for MDS. Male to female ratio was 1.2:1 for CML, 1.5:1 for JMML while in all MDS patients were males. The median duration of onset of symptoms was 2 months (1 week -16 months).

**Table 1: Classification of MPD according to PB\* and BM\*\* findings.**

| Condition             | Frequency | Percent |
|-----------------------|-----------|---------|
| CML-Chronic phase     | 22        | 44      |
| CML-Accelerated phase | 6         | 12      |
| CML-Blast crisis      | 3         | 6       |
| JMML                  | 15        | 30      |
| MDS                   | 4         | 8       |
| Total                 | 50        | 100     |

\*Peripheral blood \*\*Bone marrow

**Table 2: Demography and clinical data of the 50 MPD patients treated in CWTH 2000-2009.**

| Items                        | All | % (valid) | CML | % (valid)   | JMML | % (valid)   | MDS | %   |
|------------------------------|-----|-----------|-----|-------------|------|-------------|-----|-----|
| <b>Overall</b>               | 50  | 100       | 31  | 100         | 15   | 100         | 4   | 100 |
| <b>Age (years)</b>           |     |           |     |             |      |             |     |     |
| ≤ 2                          | 9   | 18        | 2   | 6.5         | 6    | 40          | 1   | 25  |
| <2-10                        | 24  | 48        | 15  | 48.4        | 8    | 53.3        | 1   | 25  |
| <10-15                       | 17  | 34        | 14  | 45.1        | 1    | 6.7         | 2   | 50  |
| <b>Sex</b>                   |     |           |     |             |      |             |     |     |
| Males                        | 30  | 60        | 17  | 54.8        | 9    | 60          | 4   | 100 |
| Females                      | 20  | 40        | 14  | 45.2        | 6    | 40          | --  | --  |
| <b>Duration of onset</b>     |     |           |     |             |      |             |     |     |
| <30 days                     | 12  | 24 (26.1) | 7   | 22.9 (24.1) | 3    | 20 (23.1)   | 2   | 50  |
| 1-3 months                   | 26  | 52 (56.5) | 20  | 64.5 (68.9) | 6    | 40 (46.2)   | --  | --  |
| >3 months                    | 8   | 16 (17.4) | 2   | 6.5 (6.9)   | 4    | 26.7 (30.8) | 2   | 50  |
| NR*                          | 4   | 8         | 2   | 6.5         | 2    | 13.3        |     |     |
| <b>Clinical presentation</b> |     |           |     |             |      |             |     |     |
| Pallor                       | 46  | 92        | 27  | 87          | 15   | 100         | 4   | 100 |
| Skin manifestation           | 3   | 6         | 1   | 3.2         | 1    | 6.7         | 1   | 25  |
| Fever                        | 42  | 84        | 26  | 83.9        | 13   | 86.7        | 3   | 75  |
| Bleeding                     | 11  | 22        | 8   | 25.8        | 2    | 13.3        | 1   | 25  |
| Lymphadenopathy              | 23  | 46        | 13  | 41.9        | 10   | 66.7        | 0   | --  |
| Liver ≥ 5 cm BCM             | 22  | 44        | 12  | 38.7        | 8    | 53.3        | 2   | 50  |
| Spleen ≥ 5cm BCM             | 41  | 82        | 30  | 96.8        | 10   | 66.7        | 1   | 25  |

\*NR: not recorded

Pallor was the presenting feature in 46 (92%) patients, followed by fever in 42 (84%) patients and bleeding in 11 (22%) patients while skin manifestation was found in three patients only (one from each disease). Lymphadenopathy, hepatomegaly, and splenomegaly (> 5 cm below costal margin for both liver and spleen) were found in 24 (48%) patients, 22 (44%) patients and 41 (82%) patients respectively.

Table 3 shows the profile of the initial laboratory findings; the mean and median Hb values were 7.9 g/dl and 7.5 g/dl respectively (3.7 - 14.3 g/dl), the mean and median WBC values were  $113 \times 10^9/L$  and  $71 \times 10^9/L$  (range 3 -  $455 \times 10^9/L$ ). Leukocytosis ( $WBC \geq 50 \times 10^9/L$ ) was observed in 33 (66%) cases, of which 11 (22%) patients had hyperleukocytosis ( $WBC \geq 200 \times 10^9/L$ ). Thrombocytopenia was observed in 16 (32%) patients while thrombocytosis in 6(12%).

The overall outcome of 50 patients is shown in Table 4; families of 5 (10%) refused any sort of treatment, 9 (18%) patients were referred to other centers (2 for palliative treatment, 5 to receive Imatinib from their governorates as recommended by the Ministry of Health and other two patients went abroad for BM transplant), 17 (34%) patients were lost during the follow up, 15 (30%) patients died and 4 (8%) were still alive in complete remission on Imatinib until the last date for follow up.

#### Details of the outcome

- **CML-CP:** 22 patients (1 refused any treatment, 3 died after chemotherapy (median 378 days), 1 died before treatment, 5 lost on treatment (median 81 days), 4 referred to nearby centers for treatment, 1 went for BM transplant (after 37 month on treatment), 2 went to BC then died after AML protocol, 1 went to AP (21 month on treatment) and lost, and 4 still alive in remission (median of 4.5 years).
- **CML-AP:** 6 patients (2 refused any treatment, 1 died after 2 months treatment, 2 lost after treatment (median 15.5 months), 1 went to BC then lost).

**Table 3: Initial laboratory results of 50 patients.**

| Items                         | All | %   | CML % (valid) | JMML % (valid) | MDS | %           |
|-------------------------------|-----|-----|---------------|----------------|-----|-------------|
| Overall                       | 50  | 100 | 31            | 100            | 15  | 100         |
| Hb                            |     |     |               |                |     |             |
| <7g/dl                        | 14  | 28  | 9             | 29             | 5   | 33.3        |
| 7-10g/dl                      | 26  | 52  | 17            | 54.8           | 6   | 40          |
| >10g/dl                       | 10  | 20  | 5             | 16.1           | 4   | 26.7        |
| WBC ( $\times 10^9/L$ )       |     |     |               |                |     |             |
| <50                           | 16  | 32  | 5             | 16.1           | 8   | 53.3        |
| $\geq 50$ -100                | 19  | 38  | 12            | 38.7           | 7   | 46.7        |
| >100-<200                     | 4   | 8   | 4             | 12.9           | -   | -           |
| $\geq 200$                    | 11  | 22  | 10            | 32.6           | -   | -           |
| Platelets ( $\times 10^9/L$ ) |     |     |               |                |     |             |
| <50                           | 12  | 24  | 1             | 3.2 (6.7)      | 8   | 53.3 (72.7) |
| 50 -100                       | 2   | 4   | 2             | 6.5 (8)        | -   | -           |
| <100-150                      | 2   | 4   | 1             | 3.2 (6.7)      | 1   | 6.7 (9.1)   |
| <150-450                      | 7   | 14  | 5             | 16.1 (33.3)    | 2   | 13.3 (15.4) |
| <450                          | 6   | 12  | 6             | 19.4 (24)      | -   | -           |
| NR*                           | 21  | 42  | 16            | 51.6           | 4   | 26.7        |

\*NR: Not Recorded

**Table 4: Overall outcome of 50 MPD patients treated in CWTH for the period 2000-2009.**

| Condition                         | Frequency | Percent |
|-----------------------------------|-----------|---------|
| Refused treatment                 | 5         | 10      |
| Referred to other hospitals       | 9         | 18      |
| Died                              | 15        | 30      |
| Lost to follow up                 | 17        | 34      |
| Still alive in complete remission | 4         | 8       |
| Total                             | 50        | 100     |

- **CML-BC:** 3 patients (2 lymphoid crises, one lost after finishing treatment of crises and one died after therapy; 1 myeloid crises died after therapy).
- **JMML:** 11 patients (2 refused any therapy, 2 died after treatment (median 51 days), 1 died while on supportive only, 1 went to BC and died after therapy, 3 lost while on therapy (median 55 days), 2 referred for treatment to nearby centers)
- **JMML-BC:** 4 patients (1 died 52 day post induction, 1 referred to a nearby center for supportive treatment, 2 lost before treatment).
- **MDS:** 4 patients (1 went abroad for BM transplant, 2 lost on treatment, 1 died on supportive treatment).

#### Discussion

Chronic myeloid leukemia (CML) constitutes 3% of pediatric leukemia, making evidence-based recommendations difficult. The rarity of MDS and MPD in children and the lack of a widely accepted classification have contributed to the paucity of reports on these malignancies in the pediatric literature.<sup>[9]</sup>

For this reason, all patients under the definition of myeloproliferative disorders were included in the current analysis especially that the differentiation between the groups are difficult depending on bone marrow aspirate and peripheral blood film without the cytogenetic analysis.

Chronic Myeloid Leukemia: Based on ordinary diagnostic procedures during the study period, CML incidence of 2.3% of all leukemias was similar to literature of 1-3%<sup>[13]</sup> but lower than Sinniah study of 4%<sup>[14]</sup> and HUGO study of 5%.<sup>[15]</sup>

Chronic phase CML at time of diagnosis constitutes 71% which is lower than 95% in Hugo study. On the contrary, accelerated phase and blastic crisis forms 19% and 10% respectively are much higher than 2.5% in Hugo study, this might reflect delay in presentation and diagnosis especially that all the patients in the current study were symptomatic while 23% of Hugo study were discovered incidentally. Male to female ratio in CML was 1.2:1 is lower than literature and other studies (range 1.4-1.8),<sup>[16,17]</sup> the small sample size may preclude any interpretation.

The current study shows that 80.5% of the patients were older than 5 years, this is similar to 80% reported in Golub study<sup>[16]</sup> but lower than 95% in Hugo study<sup>[15]</sup> which includes extended age group to 16 years.

Massive splenomegaly was observed in 96% of patients which is higher than HUGO study (36%) and Frédéric study (70%).<sup>[15,18]</sup> Fever and pallor were reported in 84% & 87% of patients respectively while being infrequent in HUGO study; 18% & 13% respectively.<sup>[15]</sup> This might be due to late presentation, diagnosis and referral of the patients in the current study especially those who live far places from Baghdad, and also it might be due to insidious presentation that made the family less urged for quick consultations.

The median level of Hb is 7.4 g/dl (range 3.7-11.3 g/dl) is lower than Frederic study 11.1 g/dl (range 4-14.4 g/dl).<sup>[18]</sup> Median WBC of  $87 \times 10^9/L$  are much lower than Frédéric study of  $242 \times 10^9/L$ , however the range ( $22-455 \times 10^9/L$ ) is narrower than Frederic study ( $10-720 \times 10^9/L$ ).<sup>[18]</sup> Leukocytosis (WBC  $\geq 50 \times 10^9/L$ ) was observed in 83.9% of cases in the current study lower than HUGO study of 92.3%.<sup>[15]</sup> Thrombocytosis was reported in 32% of the patients similar to HUGO study.<sup>[15]</sup> All the above observations might highlight questions regarding the exact diagnosis as we are comparing with Philadelphia positive CML studies.

Juvenile Myelomonocytic Leukemia: Median age of JMML in this study was 3 years; lower than 3.4 years in Woods' study<sup>[5]</sup> and higher than 23-24 months in other studies.<sup>[2,19]</sup> Although males were more than females with a ratio 1.5:1, other big studies showed more predominance of males of 2.7:1,<sup>[19]</sup> 2.5:1<sup>[2]</sup> this might be due to small sample in the current study or due to some differences in the behavior of disease. Patients below one year were observed in 13.3% which is lower than 35% reported in Emanuel study in USA and in literature.<sup>[2,13]</sup>

It was stressed that if a child is significantly older than 6 years, other potential diagnoses should be very strongly considered,<sup>[2]</sup> this study recorded two (13.3%) patients aged more than 6 years who need further assessment as there might be an intermingle between JMML and other types of myeloproliferative disorders.

This study showed variable forms of destiny in all groups as there was limitation in the proper diagnosis and in the management, lack of Imatinib for a variable period of time, poor socioeconomic status and complexity of the logistics to get Imatinib from a hospital nearby to patient's residence assigned by the Ministry of Health in addition to the poor prognosis of the disease, all these factors made the families of many children (44%) either refused treatment or lost to follow up after receiving a variable treatment whether chemotherapy or Imatinib or supportive care only. Mortality in this group of disorders is high (30%) in the current study and might be underestimated because 34% of patients were lost to follow up, this high incidence might be due either to late presentation of the patients or poor supportive care facilities or progressive disease due to inadequate follow up by the families.

## Conclusion

In spite of lack of definitive criteria for diagnosis of MPD due to lack of laboratory facilities, yet the clinicopathological features were comparable to other studies elsewhere. Most of

patients with MPD were symptomatic and have high percentage of aggressive behavior compared with other studies. High percentage of accelerated and blastic crisis of MPD might reflect delay in diagnosis or aggressive behavior of the disease.

## Conflict of Interest

The authors disclose that they have no conflicts of interest.

## References

1. Swerdlow, SH. International Agency for Research on Cancer, World Health Organization. WHO classification of tumours of haematopoietic and lymphoid tissues. City: International Agency for Research on Cancer; 2008.
2. Emanuel PD. Juvenile myelomonocytic leukemia and chronic myelomonocytic leukemia. *Leukemia*. 2008;22:1335-1342.
3. Vardiman JW, Thiele J, Arber DA, Brunning RD, Borowitz MJ, Porwit A, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. 2009;114:937-951.
4. Koike K, Matsuda K. Recent advances in the pathogenesis and management of juvenile myelomonocytic leukaemia. *Br J Haematol*. 2008;141:567-575.
5. Woods WG, Barnard DR, Alonzo TA, Buckley JD, Kobrinsky N, Arthur DC, et al. Prospective study of 90 children requiring treatment for juvenile myelomonocytic leukemia or myelodysplastic syndrome: a report from the Children's Cancer Group. *J Clin Oncol*. 2002;20:434-440.
6. Andolina JR, Neudorf SM, Corey SJ. How I treat childhood CML. *Blood* 2012;119:1821-1830.
7. Palandri F, Castagnetti F, Testoni N, Luatti S, Marzocchi G, Bassi S, et al. Chronic myeloid leukemia in blast crisis treated with imatinib 600 mg: outcome of the patients alive after a 6-year follow-up. 2008;93:1792-1796.
8. Pinkel D. Differentiating juvenile myelomonocytic leukemia from infectious disease. *Blood*. 1998;91:365-367.
9. Hasle H. Myelodysplastic and myeloproliferative disorders in children. *Curr Opin Pediatr*. 2007;19:1-8.
10. Hann I, Vora A, Richards S, Hill F, Gibson B, Lilleyman J, et al. Benefit of intensified treatment for all children with acute lymphoblastic leukaemia: Results from MRC UKALL XI and MRC ALL 97 randomised trials. UK Medical Research Council's Working Party on Childhood Leukaemia. *Leukemia*. 2000;14:356-363.
11. Medical Research Council, Working party on leukemia in childhood. *Acute Myeloid Leukemia Trial 12*. 1955.
12. Nourusis MJ. APSS statistical software. SPSS:Base and Advanced statistics 13.0. Chicago, USA. SPSS Inc, 2004.
13. Ashok S. Myeloproliferative disorders. In: Lanzkowsky P, editor. *Manual of Pediatric Hematology and Oncology*. 5th ed. Elsevier Academic press, USA. 2011;503-510.
14. Sinniah D, Peng LH. Malaysian childhood leukemia: A 13 year review at the University Hospital, Kuala Lumpur. *Leuk Res*. 1981;5:271-278.
15. Hugo CM, Gerard S. Philadelphia Chromosome-Positive Chronic Myelocytic Leukemia in Children Survival and Prognostic Factors. *Cancer*. 1983;52:721-727.
16. Golub TR, Arceci RJ. Acute Myelogenous Leukemia. In: Pizzo PA, Poplack DG, editors. *Principles and Practice of Pediatric*

- Oncology. 4th edn. Philadelphia (Ph): Lippincott Williams & Wilkins Publishers; 2001;545-550.
17. Ries LAG SM, Gurney JG, Linet M, Tamra T, Young JL, Bunin GR (eds). Cancer Incidence and Survival Among Children and Adolescents: United States SEER Program 1975-1995 (NIH publication no. 99-4649). Bethesda, MD: National Cancer Institute, SEER Program; 1999.
  18. Frédéric M, Philippe T. Clinical and biological features at diagnosis in 40 children with chronic myeloid leukemia. *Blood*. 2008;101:376
  19. Passmore SJ, Chessells JM, Kempski H, Hann IM, Brownbill PA, Stiller CA. Paediatric myelodysplastic syndromes and juvenile myelomonocytic leukaemia in the UK: A population-based study of incidence and survival. *Br J Haematol*. 2003;121:758-767.