Refractory Anemia in Childhood: A Retrospective Analysis of 67 Cases with Particular Reference to Monosomy 7

Short running title: Refractory anemia in childhood


Institutions:
VU University Medical Center Amsterdam, The Netherlands; Department of Pathology, University of Erlangen; Childhood Cancer Research Group, Oxford, UK; IRCCS Policlinico S. Matteo, Pavia, Italy; Skejby Hospital, University of Aarhus, Denmark; Department of Pediatrics, University of British Columbia, Canada; Department of Pediatrics, 2nd Medical Faculty, Charles University, Prague, Czech Republic; Department of Pediatrics and Pathology, University of Freiburg, Germany; Department of Pediatrics, University of Gießen, Germany; Department of Haematology and Oncology, Great Ormond Street Children’s Hospital, London, UK; Cattedra di Ematologia, University La Sapienza of Roma, Italy; Laboratory Department, Istituti Clinici di Perfezionamento, Milano, Italy; Department of Pathology, University of Odense, Denmark; Dutch Children Leukemia Study Group, The Hague, The Netherlands

Grant support:
This work was supported, in part, by the Deutsche José Carreras Stiftung e.V. and the BMBF Competence Net “Pediatric Oncology”, by the grant of the Ministry of Health of the Czech Republic IGA NE 5676-4.

Corresponding author:
Charlotte M. Niemeyer, Division of Hematology and Oncology, Department of Pediatrics and Adolescent Medicine, Mathildenstrasse 1, 79106 Freiburg, Germany
Phone:-49-761-270-4506, Fax:-49-761-270-4518, email: niemeyer@kikli.ukl.uni-freiburg.de

Word count: 3802
Abstract

Primary myelodysplasia (MDS) without an increased number of blasts is a rare finding in childhood. We have performed a retrospective analysis of 67 children with a diagnosis of primary MDS to determine their clinical and hematological course. The median age at diagnosis was 8.3 years (range 0.3 – 18.1). In contrast to refractory anemia in adults, 44% of patients had hemoglobin greater than 10 g/100mL. The median white blood count and absolute neutrophil count were 3.6 and 0.9 x10^9/L, respectively. Seventy-five percent of patients were thrombocytopenic. The bone marrow was hypocellular in 43% of cases. The results of cytogenetic analysis showed monosomy 7 in 49% of patients, trisomy 8 in 9% and other abnormalities in 9%. The probability of survival 10 years after diagnosis was 0.48 (standard error [SE] = 0.10). Patients with monosomy 7 had a significantly higher estimated probability of progression to advanced MDS as compared to patients with other chromosomal anomalies or normal karyotype. Of the 67 children, 41 received an allogeneic stem cell transplant (SCT). Patients who had not progressed to advanced MDS prior to SCT had a significantly greater probability of survival than patients who suffered progression (0.76 [S.E. = 0.09] versus 0.36 [S.E. = 0.16]). SCT improved outcome for patients with monosomy 7 and should be offered early in the course of the disease. Recommendations for best treatment options for children with other chromosomal abnormalities or normal karyotype may have to wait results of prospective clinical trials.

niemeyer@kikli.ukl.uni-freiburg.de

Word count: 244
Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of acquired hematopoietic stem cell disorders characterized by peripheral blood cytopenia, ineffective and dysplastic hematopoiesis and a varying propensity to undergo leukemic transformation. The natural history of the disease is influenced by the number of blasts in the bone marrow. In adults, MDS without increased number of blasts and low risk of leukemic progression is usually characterized by anemia and a normo- or hypercellular marrow with erythroid hyperplasia. The FAB group coined the term “refractory anemia” (RA) for these disorders.¹ This nomenclature has been accepted in the recent WHO classification.²

In childhood, MDS with less than 5% blasts in the bone marrow is particularly difficult to diagnose, because dysplasia of hematopoietic cells is frequently observed during infections, in metabolic disorders, nutritional deficiencies and a variety of other diseases.³⁻⁶ Following treatment of the underlying disorder, these dysplastic changes generally resolve. The presence of a cytogenetic abnormality in hematopoietic cells is helpful in confirming a diagnosis of MDS, but in the absence of such an abnormality the diagnosis is difficult. We have retrospectively reviewed the clinical and laboratory findings in a group of 67 children with refractory anemia to determine the natural history of the disease and to identify prognostic factors for disease progression and outcome.
Patients and Methods

Data of 67 children below the age of 19 years with a diagnosis of RA from Canada (n=4), Czech Republic (n=2), Denmark (n=8), Germany (n=18), Italy (n=9), The Netherlands (n=9) and the United Kingdom (n=17) were analyzed. Diagnosis, clinical and hematological data of all patients included had been reviewed nationally by the respective cooperative groups. Patients with preceding constitutional bone marrow failure disorders, known constitutional chromosomal abnormalities and previous chemo- or radiotherapy were excluded. To rule out Fanconi anemia, hypersensitivity testing to DNA cross-linking agents had been performed in most patients. Due to different national review structures, accrual times and age at diagnosis varied between nations. Overall accrual was from December 1979 to June 1998. Data were analyzed as of April 28, 2001. Data on 21 patients included in this series have been reported previously by the authors. Follow-up was available for all patients included into the study.

Due to the retrospective nature of the study, several patients had missing data for some of the parameters studied. For patients with missing data for white blood count (WBC), platelet count (plt), hemoglobin (Hb) or peripheral blood (PB) differential count at the time of diagnosis values for later time points had been reported. Normal ranges for mean corpuscular volume (MCV) of red blood cells according to age were modified according to Dallman. The 2 patients without an evaluable bone marrow (BM) aspirate at the time of diagnosis had BM biopsies indicative of RA. Biopsies had been performed in 50 patients. BM cellularity was judged on biopsies. For the 17 patients without a biopsy, the aspirate showed a reduced cell number in 5 cases. These 5 patients had
been classified as MDS because of the presence of dysplasia in at least 2 cell lines and 4 of the 5 patients had an abnormal karyotype. Data on dysplasia scores for myelopoiesis, erythropoiesis and megakaryopoiesis was available for 61, 64 and 58 patients, respectively. Chromosomal analyses of BM cells were performed by standard techniques by the national reference laboratories or by the local treatment center. For correlation between karyotype and clinical findings, patients were subdivided in 3 karyotype groups as follows: normal karyotype, monosomy 7, trisomy 8 or other cytogenetic abnormalities.

Overall survival was calculated from the date of diagnosis to the date of death or last follow-up. Advanced MDS was defined as a sustained increase in BM blasts ≥ 5%. Time to progression to advanced MDS was defined as the time from date of the diagnosis of RA to the date of progression to more advanced MDS. To calculate the risk of progression, patients who had received a stem cell transplantation (SCT) prior to progression were censored at the time of allograft. The survival after SCT was calculated from the date of SCT to the date of death or last follow-up.

The Kaplan-Meier method was used to estimate survival rates. Standard errors were calculated using Greenwoods formula. The two-sided log-rank test was used to test the equality of the survivorship functions in different subgroups. To acknowledge the presence of competing risks, the incidence of progression to advanced MDS was expressed as cumulative hazard rates. The Kruskal-Wallis H test is used to compare the medians of 3 or more groups (Post hoc test: Mann Whitney U-Test). Spearman's Rank Correlation (ordinal data) and Cramér's V (categorical data) were used to analyze associations between prognostic factors.
Results

Clinical Presentation

There were 30 boys and 37 girls diagnosed with RA. The median age at diagnosis was 8.3 years (range 0.3 – 18.1). The most common presenting symptoms were malaise (60%), bleeding (45%), fever (22%) and infection (21%). For 19% of patients, no clinical signs or symptoms were reported. Two patients, both with monosomy 7, had been diagnosed during work-up for BM donation for a sibling transplant. Lymphadenopathy, most likely due to infections, was seen in 4 patients; 1 child had a slightly enlarged spleen. None of the patients had hepatomegaly. Congenital abnormalities were observed in 9 patients (13%). They included a Dandy Walker malformation (2 patients), von Willebrand’s disease type 2, dysmorphic features with mental retardation or with congenital heart disease, pes equino varus, hypermelanosis, platelet storage pool disorder and factor XI deficiency. Median interval between the onset of symptoms and diagnosis was 3.5 months (range 0-84).

Hematological data

At diagnosis, median WBC was 3.6 x10^9/L (Fig. 1). Severe neutropenia was noted in 27% of patients (Fig. 2). In 2 patients, PB monocytopsis (> 1x10^9/L) was present in the absence of organomegaly or clinical course indicative of chronic myelomonocytic leukemia. An increase in PB eosinophils and basophils (>5%) was seen in 6 and 1 patients, respectively. Two patients had an absolute eosinophil count exceeding 1 x10^9/L. Most patients were thrombocytopenic; 75% had a platelet count below 150 x10^9/L (Fig. 2). The hemoglobin concentration and reticulocyte count varied over a wide range.
Figure 1. Hematological data in peripheral blood at diagnosis

The Box Plots show the graphic display of the median $x$, 1st quartile (25%) and 3rd quartile (75%), the non-outlier range, outliers (o) and extreme values (*).

WBC, white blood count; ANC, absolute neutrophil count; Hb, hemoglobin; Reti, reticulocyte; MCV, mean corpuscular volume of red cells; HbF fetal hemoglobin;

Fifty-six per cent of patients had Hb below 10 g/100mL, and 11% Hb within the normal range (Fig. 2).

Figure 2. Absolute neutrophil count, hemoglobin and platelet count at the time of diagnosis

ANC, absolute neutrophil count
Macrocytosis of red blood cells evaluated according to patient age was seen in 75% of children, and HbF elevated in 82% of the 28 patients in whom it was measured. There was no correlation between HbF and MCV, BM cellularity or karyotype.

BM cellularity was increased in 25% of patients, normal in 33% and reduced in 43%. Within the 3 groups with hyper-, normo- and hypocellular BM, the median WBC was 4.7 x 10^9/L, 3.4 x 10^9/L and 2.7 x 10^9/L, respectively (p<0.01). There were no differences between the 3 groups with respect to other PB parameters, karyotype or survival. Erythroid predominance with a ratio of myelopoiesis to erythropoiesis < 1 was noted in 45% of patients. Dysplasia of red cells, white cells and megakaryocytes was reported in 85%, 58% and 58% of cases, respectively. Presence of dysplasia did not correlate with progression to advanced MDS.

**Chromosomal abnormalities**

Data on karyotype of BM cells at diagnosis were available in 66 of the 67 patients. The karyotype was normal in 22 children, while 32 patients had monosomy 7, 6 trisomy 8 and 6 other aberrations. Among the 6 children with a chromosomal abnormality other than monosomy 7 or trisomy 8, 2 had a loss of 7q material. Two of the patients with monosomy 7 and 3 of the patients with trisomy 8 had additional abnormalities. There were no differences among patients with normal karyotype, monosomy 7 or trisomy 8 and other abnormalities with respect to age, sex, median values for WBC, ANC, Plt, MCV, HbF or BM cellularity. Patients with monosomy 7 had a significantly higher Hb (median 10.6, range 4.1-12.6) as compared to patients with normal karyotype (median 8.5, range 3.5-14.5) (p<0.01).
Serial chromosomal studies were performed in 44 patients with a median of 4 (range 2-14) analyses per patient. The original chromosomal aberrations persisted over time in all patients. Karyotypic evolution was noted in 5 cases (see Tab. 1 for details).

### Table 1. List of chromosomal abnormalities other than monosomy 7 only

* karyotypic evolution; #, karyotype was interpreted as 7q- abnormality

With exception of children with normal karyotype, the original aberrations remained in all patients. In each case, karyotypic evolution was accompanied by progression to advanced MDS. Abnormal karyotypes other than monosomy 7 alone are listed in Table 1.
Clinical course and progression to more advanced stages of MDS

At time of analysis, 25 patients had died and 42 were alive (Fig. 3). Overall survival at 10 years was 0.48, \( [SE] = 0.10 \). Four children had died within 0.1–12 months from diagnosis due to complications of pancytopenia prior to any specific therapy or progression to advanced MDS. Two additional children succumbed to intensive chemotherapy delivered for RA in the absence of disease progression. Twelve patients were alive with stable disease without SCT (Fig. 3). Of the 29 children transplanted prior to progression of MDS, 23 were alive. Twenty patients had progressed to advanced MDS. Of those, 12 had been transplanted and 8 had received intensive chemotherapy only. In total, 13 children had received intensive chemotherapy. G-CSF prior to intensive therapy or SCT had been administered to 3 patients; 4 children had been treated with immunosuppressive therapy consisting of cyclosporin and anti-thymocyte globulin.

Figure 3. Flow-sheet indicating the clinical course and outcome children with refractory anemia

Numbers given refer to the total study population irrespective of karyotype (“all”) and to patients with monosomy 7 (-7).
For the 20 patients with progression to advanced MDS median time to progression was 1.7 years (0.2-5.3). The cumulative incidence of progression was significantly higher for patients with monosomy 7 compared to patients with other chromosomal abnormalities or normal karyotype (Fig. 4).

![Graph showing cumulative incidence of progression to advanced MDS](chart.png)

**Figure 4. Cumulative incidence of progression to advanced MDS for patients with refractory anemia and either normal karyotype, monosomy 7, or trisomy 8 or other abnormalities at the time of diagnosis**

Patients who had received stem cell transplantation were censored at time of transplantation.

**Stem cell transplantation**

Of the 67 children, 41 received an allogeneic SCT at a median time of 16 months (range 1-124) from diagnosis. In 17 transplants the donor was an HLA compatible family donor (MFD), in 24 cases an unrelated volunteer (MUD). Source of stem cells was bone marrow, peripheral blood or umbilical cord in 34, 5 and 2 patients, respectively. Preparative regimens varied widely and included total body irradiation (TBI) in 21 patients and busulfan in the remaining 20. Following SCT, 28 patients are alive, 2 relapsed and 11 died due to transplant related causes. The latter included graft failure.
(n=2), graft versus host disease (n=4), infection (n=4) and thrombocytopenic purpura (n=1). Probability of survival at 6 years was 0.64 ± 0.18 for the 41 children (Fig. 5), with results for patients grafted from either a MFD or a MUD being 0.73 ± 0.24 and 0.55 ± 0.25, respectively (p=n.s.). There was no difference in outcome following SCT according to year of transplantation, although it has to be considered that more MUD transplants were performed since 1995 compared to the earlier years (p=0.03).

Figure 5. Survival from the time of stem cell transplantation for children diagnosed with refractory anemia with or without progression to advanced MDS prior to stem cell transplantation

The upper panel gives the data for all children irrespective of karyotype, the lower panel for children with monosomy 7.
Twelve patients had suffered progression to advanced MDS prior to SCT at a median of 6 months (range 1-27) from diagnosis. Patients without progression prior to SCT had a significantly better probability of survival than patients who had progressed (p = 0.03, Fig. 5). Two patients relapsed after SCT, both had monosomy 7. One of these patients had been transplanted with the diagnosis of RA, the other suffered progression prior to SCT. There were no significant differences in survival following SCT according to karyotype.

**Survival according to karyotype**

Comparing survival according to karyotype at time of diagnosis there was no statistical significant difference among patients with normal karyotype, monosomy 7 or trisomy 8 or other karyotype (Fig. 6). However, including the 2 patients with normal karyotype who subsequently developed a karyotypic abnormality in the respective karyotype groups, survival in patient with persistently normal karyotype was significantly better compared to that of patient with monosomy 7 (p=0.02) but not compared to that of a patients with other karyotypes.

![Survival from the time of diagnosis for 66 children diagnosed with refractory anemia according to karyotype](image-url)
Without SCT patients with monosomy 7 had a poor survival (Tab. 2). Children with trisomy 8 or other karyotypes who were grafted tended to have a lower WBC, be more often platelet transfusion dependent and have more often a hypocellular BM as compared to non-grafted patients.

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>% alive</th>
<th>dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>22</td>
<td>33</td>
<td>17</td>
</tr>
<tr>
<td>Monosomy 7</td>
<td>32</td>
<td>49</td>
<td>16</td>
</tr>
<tr>
<td>Trisomy 8 or other abnormalities</td>
<td>12</td>
<td>18</td>
<td>9</td>
</tr>
</tbody>
</table>

**Table 2. Patient distribution and outcome according to karyotype groups**

In part A, data for all 66 patients with available karyotype are given. In part B, data are listed according to stem cell transplantation (SCT) for patients with available karyotype and a follow-up of more than 16 months. Because median time from diagnosis to SCT was 16 months, nine patients with a follow-up less than 16 months had been excluded from the analysis in B (patients with normal karyotype n=2, monosomy 7 n=6, other abnormalities n=1).

Four of the 12 patients with trisomy 8 or other abnormalities were alive with stable disease without SCT at 2.2, 2.3, 3.2 and 7.9 years following diagnosis.
Discussion

Patients with RA as defined by the FAB cooperative group for disorders are usually over the age of 50 years, anemia being the main presenting symptom. The low hemoglobin is associated with reticulocytopenia, dyserythropoiesis and infrequently dysgranulopoiesis. Occasionally, other cytopenias are present at diagnosis. Children differ in their hematological presentation since neutropenia and thrombocytopenia are more frequently observed at diagnosis. In our cohort, more than half of the patients presented with an ANC < 1.0 x 10^9/L and/or a platelet count < 100 x 10^9/L. Although the term anemia, like in aplastic anemia or Fanconi anemia, is often used for pancytopenic states, we suggest that the term refractory cytopenia (RC) is more appropriate for this group of MDS patients and will be used from here on.

Cytopenia due to ineffective hematopoiesis in a hyper– or normocellular bone marrow is a hallmark of MDS. Bone marrow cellularity is generally estimated on biopsy specimens. In the study presented here, biopsies had not been performed in all patients. Taken this limitation into account, 39% of children with RC had a reduced cellularity, a percentage similar to that reported for RA in some of the adult series. However, we excluded RC evolving from acquired or constitutional bone marrow failure disorders from the study so marrow hypocellularity may be more frequent among all cases of low grade MDS in childhood. There was no correlation between cellularity and karyotype.

In the FAB classification RA was defined as having dysplasia largely restricted to the erythroid line. The recently proposed WHO classification continued to define RA as a
disorder involving the erythroid lineage only, but separated cases with presence of dysplastic features in the cells of 2 or more cell lines.\textsuperscript{2} The latter cases have been shown to have a worse prognosis due to marrow failure or leukemic progression.\textsuperscript{27,28} In our study more than half of the patients had granulocytic and/or megakaryocytic dysplasia. There was, however, no correlation between lineage dysplasia and disease progression. Prospective studies on childhood RC will clarify whether dysplasia in 2 or more cell lines is of prognostic relevance.

While dysplastic features were most often observed in the red cell precursors, erythroid hyperplasia was present in 45\% of children only. Macrocytosis of red cells, a finding characteristic of RA\textsuperscript{29}, was noted in three quarter of the patients, while Hb F was elevated in about 80\% of the patients in whom it was measured. In contrast to juvenile myelomonocytic leukemia (JMML), there was no correlation between MCV or HbF and karyotype. Interestingly, children with RC and monosomy 7 presented with a significantly higher Hb concentration compared to patients with a normal karyotype, a finding not observed in the JMML group.\textsuperscript{30}

The pathogenesis of MDS remains largely obscure. Although chromosomal changes are not thought to be initiating events, they are probably involved in disease progression. Karyotypic evolution, noted here in 5 of the 44 patients with serial chromosomal studies, was accompanied by progression to more advanced forms of MDS in each case. Of the 21 patients with a normal karyotype at diagnosis and follow-up studies, 2 subsequently developed a chromosomal aberration. Serial chromosomal analyses are helpful in assessment of children with RC.
The frequency of chromosomal abnormalities varies between FAB types of MDS. In adult RA, karyotypic changes are seen in approximately 20%-30%. In this series, chromosomal aberrations were noted in 67% of children in whom results of standard cytogenetic studies were available. This result has, however, to be interpreted with caution. The presence of a cytogenetic abnormality can be an important mean to confirm the diagnosis of MDS. Because of the difficulty in establishing the diagnosis of childhood RC, it is likely that patients with chromosomal changes were preferentially reported in this retrospective study. Furthermore, patients with monosomy 7 may be overrepresented, because some of these cases had previously been collected and analyzed. Nevertheless, our results confirm reports of other investigators indicating that monosomy 7 is the most common cytogenetic abnormality in childhood RC. In contrast, monosomy 7 is noted in less than 5% of adult RA.

While in adult MDS, monosomy 7 is frequently accompanied by multiple karyotypic rearrangements, in childhood it is often the sole abnormality; additional changes were noted in only 5 of 33 cases analyzed here. It is of interest, that 2 children with monosomy 7 were diagnosed of MDS during work-up for bone marrow harvest in view of sibling transplantation. Familial predisposition for MDS is not infrequent and may be associated with loss of chromosome 7 or partial deletion of its long arm. Morphological and cytogenetic examinations of bone marrow cells is recommended for all potential sibling donors of MDS patients.

The second most frequent chromosomal abnormality in our series was trisomy 8 (9%), which may occur with similar frequency in children and adults with MDS. Loss of the long arm of chromosome 5 (5q-), the most frequent chromosomal aberrations in adults
with RA\textsuperscript{31,35}, is exceedingly rare in childhood\textsuperscript{37} and was not observed in any of our patients.

Karyotype was the most important prognostic factor for progression to advanced MDS and survival. The estimated median time to progression for children with RC and monosomy 7 was 1.9 years. SCT in patients with RC and monosomy 7 early in the course of the disease and prior to progression was accompanied by a better post-transplant survival. Of the 13 children with monosomy 7 who were grafted without increased number of blasts, one relapsed, 3 died due to toxicity and 9 are alive without disease. Although monosomy 7 is generally considered a poor prognostic predictor irrespective of therapy\textsuperscript{35,38}, our data indicate that monosomy 7 may not have a negative impact on survival after SCT for childhood RC. Two children with RC and monosomy 7 were treated with intensive chemotherapy in the absence of disease progression. Both succumbed to therapy complications. There is no evidence that intensive chemotherapy has a role in the management of children with RC. Whether cytoreductive therapy prior to SCT for more advanced forms of MDS improves survival remains controversial.

In contrast to monosomy 7, only 4 of the 22 patients with a normal karyotype suffered progression to more advanced MDS. This low rate of leukemic transformation may raise the question whether some of these children had an unrecognized constitutional disorder with dysplasia and marrow failure rather than acquired MDS. In the absence of chromosomal changes or other markers of clonality the diagnosis of RC is difficult and it is important to define minimum diagnostic criteria in this group of patients.\textsuperscript{21} Twelve of the 22 children with RC and normal karyotype were grafted. Although we did not collect data on the clinical course of peripheral blood counts, one can assume, that children
who received a SCT had experienced more severe cytopenia. SCT might be the only curative therapy option for this patient group, but other treatment modalities like immunosuppressive therapy\textsuperscript{39,40} or the use of hematopoietic growth factors\textsuperscript{41,42} have not been systematically studied in this pediatric patient cohort. It is of note, that 4 of the 67 study patients died due to pancytopenia within one year after diagnosis. In the absence of a suitable stem cell donor, these alternative therapy approaches might be offered to children with RC endangered by severe cytopenia.

The overall survival of the 67 children was $0.48 \pm 0.20$ at 10 years. For patients with monosomy 7 or disease progression, survival was largely depended on outcome after SCT. Similar to what has been observed for young patients in other series\textsuperscript{43,44}, the probability of survival of the 29 children transplanted prior to progression to advanced MDS was $0.76 \pm 0.18$. Because transplant related toxicity is the major cause of death\textsuperscript{43,45}, preparative regimens with reduced intensity are attractive, but could increase the relapse rate.\textsuperscript{46}

The results from this largest series of childhood RC clearly indicate, that children with RC and monosomy 7 should be offered SCT early in the course of their disease. Spontaneous disappearance of monosomy 7 and cytopenia has been noted in some infants\textsuperscript{47}, but remains a rare event. Karyotype analyses in our study and in previous reports were based on standard metaphase banding cytogenetics. The significance of small monosomy 7 clones detected by fluorescence in situ hybridization (FISH) only, remains to be determined.\textsuperscript{48} Because of small patient numbers and variable outcome, recommendations on therapy for RC with chromosomal changes other than monosomy 7 cannot be drawn from this retrospective study. In the presence of a normal karyotype,
a substantial proportion of children with RC will experience a long stable course of their
disease. An expectant approach with careful observation may be reasonable care for
these patients in the absence of transfusion requirements, severe cytopenia or
infections. 49 SCT early in the course of the disease has generally been reserved for
patients with a matched sibling donor. Since results of MUD transplants have improved
and are becoming comparable to those reported for MFD grafts, early referral for SCT
prior to prolonged cytopenia or disease progression has been recommended
recently. 50,51 Future prospective multi-center trials will have to identify prognostic factors
for disease progression and define the subgroup of these children with RC and normal
karyotype that will benefit from early SCT.
Acknowledgement

The authors thank the patients and families and the physicians who referred the patients. We acknowledge the work of Charles Stiller, Pat Brownbill and Janette Wallis for their help with the UK MDS registry.
References


Refractory anemia in childhood: a retrospective analysis of 67 cases with particular reference to monosomy 7

Gabriela Kardos, Irith Baumann, S Jane Passmore, Franco Locatelli, Henrik Hasle, Kirk R Schultz, Jan Stary, Annette Schmitt-Graeff, Alexandra Fischer, Jochen Harbott, Judith M Chessells, Ian Hann, Susanna Fenu, Angelo Cantu Ragnoli, Gitte Kerndrup, Elisabeth van Wering, Tim Rogge, Peter Noellke and Charlotte M Niemeyer