Pediatric Myelodysplasia: A Study of 68 Children and a New Prognostic Scoring System

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Clinical, morphologic, and cytogenetic features were examined in a group of 68 children with myelodysplasia (MDS) referred to a single institution between 1971-1991. The morphologic French-American-British (FAB) system of classification proved of limited value in this group of patients because 50% of the cases were categorized as chronic myelomonocytic leukemia and three patients with eosinophilia and MDS were unclassifiable. Cytogenetic analysis was performed in 63 cases and clonal abnormalities were detected in 55%; the most common chromosome involved was number 7. Modification of the FAB system to incorporate additional diagnostic features such as pretreatment fetal hemoglobin (Hb F) and cytogenetics allowed incorporation of the categories of juvenile chronic myeloid leukemia (JCML) and infantile monosomy 7 syndrome (IMo7). The resulting groups of patients had highly significant differences in survival ($P = .00009$). The overall 5-year survival for the patients was 31.9% (95% CI 21.7 to 44.1) and factors influencing prognosis included: modified FAB type, platelet count, Hb F level, and cytogenetic complexity. We developed a scoring system ("FPF") when each of the following findings at diagnosis scored one point: HbF greater than 10%, platelets $\leq 40 \times 10^9/L$, and complex karyotypic changes (two or more clonal structural/numerical abnormalities), which produced groups with highly significant differences, patients with a score of 0 having a 5-year survival of 61.6% (CI 33% to 84%), whereas those with a score of two or three all died within 4 years of diagnosis. The revised classification and scoring system may prove helpful in making treatment choices in pediatric MDS and now needs to be tested prospectively in large scale population-based studies. © 1995 by The American Society of Hematology.

Materials and Methods

We reviewed the clinical information and laboratory data on all the patients referred to the Hospital For Sick Children (HSC), Great Ormond Street, during 1971-1991 in whom a diagnosis of MDS or chronic myeloproliferative disease had been made. The distinction between patients with acute myeloid leukemia (AML) and these diseases can be a fine one, but our patients with AML seen during the same period had been recently reviewed so we were able to make a systematic attempt to separate the two disorders. We excluded all children who fulfilled the criteria for a primary diagnosis of AML or who had clinical, laboratory, and cytogenetic features of Philadelphia chromosome positive chronic granulocytic leukemia (Ph1 positive CGL) and the one patient with therapy-related MDS. We identified a total of 68 patients.

Bone marrow aspirates were reviewed, blind, by three of us, without reference to the clinical findings. Blood films were available from 51 patients (it was not possible to find good quality films for the remainder) and were similarly reviewed; for all patients the results of full blood count including differential leukocyte count at the time of presentation were available. An attempt was made to classify each patient according to the FAB system as refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess of blasts (RAEB), refractory anemia with excess of blasts in transformation (RAEBT), or chronic myelomonocytic leukemia (CMML). Bone marrow trephine biopsy samples were available for 32 children, and these were reviewed to determine the cellularity and the presence of fibrosis and abnormal location of immature precursor cells (ALIP).

Cytogenetics. Cells were obtained for analysis from bone marrow samples incubated at 37°C for 1 to 2 hours or overnight in tissue culture medium containing 10% fetal calf serum. Cultures were harvested and metaphase chromosomes G-banded using standard procedures. Descriptions of karyotypes follow ISCN (1991).

A cytogenetic complexity score was devised based on the presence or absence of clonal abnormalities and their complexity at the time of diagnosis. Cases with no detectable clonal abnormalities scored 0, a score of one was given to cases having simple abnormalities arising from one event ie, single translocation, other structural abnormality, or gain or loss of one chromosome. A score of two was
PEDIATRIC MDS: A STUDY OF 68 CASES

Table 1. Children With MDS and Other Clinical Abnormalities

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/SEX</th>
<th>FAB Type</th>
<th>Associated Abnormalities</th>
<th>Treatment Type</th>
<th>Survival (mo) From Diagnosis of MDS</th>
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<tbody>
<tr>
<td>1</td>
<td>77/M</td>
<td>RA</td>
<td>Shwachman’s syndrome</td>
<td>Supportive care</td>
<td>74*</td>
</tr>
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<td>2</td>
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<td>RAEB</td>
<td>Shwachman’s syndrome</td>
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<td>42</td>
</tr>
<tr>
<td>3</td>
<td>52/M</td>
<td>RAEB</td>
<td>Shwachman’s syndrome</td>
<td>Lost to follow-up</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
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<td>RAEBT</td>
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</tr>
<tr>
<td>5</td>
<td>75/F</td>
<td>RA</td>
<td>Platelet storage pool disorder (PSPD)</td>
<td>BMT</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>71/F</td>
<td>RARS</td>
<td>PSPD and family history of malignancy</td>
<td>MUD</td>
<td>15</td>
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<tr>
<td>7</td>
<td>35/F</td>
<td>RAEBT</td>
<td>PSPD and family history of malignancy</td>
<td>ABMT</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>36/M</td>
<td>CMML</td>
<td>Classical type 1 neurofibromatosis</td>
<td>Supportive care</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>3/F</td>
<td>CMML</td>
<td>Cafe au lait spots; no other stigmata of neurofibromatosis</td>
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<td>78*</td>
</tr>
<tr>
<td>10</td>
<td>1.5/F</td>
<td>CMML</td>
<td>Multiple congenital abnormalities including coloboma and low IQ. Brother, same problems</td>
<td>Splenectomy</td>
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</tr>
<tr>
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<td>Constitutional t(6;16)(p10;q10)</td>
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<td>106*</td>
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<tr>
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<td>CMML</td>
<td>Constitutional t(6;16)(p10;q10)</td>
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<td>5</td>
</tr>
<tr>
<td>13</td>
<td>72/M</td>
<td>CMML</td>
<td>Short stature</td>
<td>BMT</td>
<td>8</td>
</tr>
<tr>
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<td>Short stature</td>
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<td>Developmental delay and xanthomata</td>
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<td>Pierre Robin syndrome and ventricular septal defect</td>
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<td>Pulmonary stenosis</td>
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<td>CMML</td>
<td>Xanthogranulomata</td>
<td>MUD</td>
<td>6</td>
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</tbody>
</table>

Abbreviations: BMT, bone marrow transplant (allogeneic); MUD, matched unrelated donor transplant; ABMT, intensive chemotherapy plus autologous bone marrow transplant; NIC, non-intensive chemotherapy (prednisolone ± 6-mercaptopurine).

* Still alive.

given to complex abnormalities arising from two or more structural or numerical events.

We applied both the original and revised Bournemouth scoring systems to assess their value in predicting prognosis in pediatric patients.

We related the FAB classification to the clinical classification for two well described subgroups of pediatric MDS, namely JCM and IMo7. Patients were classed as having JCM if they had CMML morphology and raised fetal hemoglobin (HbF) (>10%), and did not have monosomy 7. Patients with Shwachman’s syndrome may have a raised HbF, but did not have morphologic CMML. Monosomy 7 is a common finding in myelodysplasia of both children and adults, but the children classified as having IMo7 in this series were under 4 years of age at presentation with any type of myelodysplasia and monosomy 7. All older children with MDS, who happened to have this cytogenetic finding, were excluded from this definition and classified according to the morphologic (FAB) type.

Standard nonparametric methods were used to analyze the relationship between different characteristics of the study population. Actuarial survival rates were calculated by Kaplan-Meier methods and the differences between survival curves analyzed by the log-rank test using the Sareal program. All survivors, except three patients who had been referred from abroad, had been followed until June 1994. The minimum follow-up period was 33 months from the time of diagnosis.

RESULTS

Clinical findings. There were 46 males and 22 females, with a median age of 37 months (range, 7 weeks to 11.8 years). The median duration of symptoms before referral was 3 months (range, 0 to 108 months).

Nineteen of the patients had other clinical abnormalities in addition to MDS, and these are shown in Table 1. Most of the abnormalities associated with MDS have been described previously. Four patients had Shwachman’s syndrome. Cases 5 through 7 were members of different families with inherited platelet storage pool defects (PSPD). Two of these families had an increased incidence of malignancy; the family tree of case 6, the only child in the series with RARS, is shown in Fig 1, whereas case 7 had a sibling with a brain tumor. Case 8 had neurofibromatosis (NF) in association with CMML (which would be clinically classified as JCM), whereas case 9 had cafe au lait spots, but no other stigmata of NF. There were two pairs of siblings with MDS. Case 10 had multiple congenital abnormalities and CMML, her elder brother had the same diagnoses made before the start of our study period and is excluded. Cases 11 and 12 were male twins, both with CMML and a constitutional chromosomal...
abnormality t(7;16)(p10;q10); their father also had this translocation, but no hematologic abnormality. The remaining seven cases had a variety of other clinical abnormalities.

There was no discernible association of particular FAB types with any congenital abnormality except for the association of NF with CMML. There were no cases of CMML in the patients with Shwachman’s syndrome or PSPD.

Morphology. We were able to assign FAB types on the basis of blood and bone marrow findings to most of the patients. Three children were unclassifiable; all had mild to moderate marrow dysplasia and marked eosinophilia (25% to 42%) in both blood and marrow, and one child had marked skin infiltration. We have classified these children as having eosinophilic MDS; two were female and one male, ages 6, 42, and 99 months, respectively. Two of these cases of MDS with eosinophilia have been published.

The largest group of 35 children, 29 males and six females, were classified as CMML and, with a median age at diagnosis of 13 months, (range, 1.7 to 113) were significantly younger than the other groups combined (median 75 months, P = 0.0001 by the Mann-Whitney test). Refractory anemia and RAEB were the next most common subtypes (11 and 13, respectively); there were four cases of RAEBT and only one of RARS. There was no particular pattern of age and sex distribution in these groups.

Trehine biopsies from 32 patients were available for review. There was good agreement with the cellularity of the marrow aspirate in the 28 cases in which this comparison could be made. It was possible to examine the trephines for the presence of ALIPS in 26 of the specimens, but there was no correlation with this finding and any FAB subtype. Moderate or marked fibrosis was seen in 21 of 26 (81%) of the trephines stained for reticulin.

Cytogenetics. Chromosome data were available from 63 cases, of these, 35 (55%) had clonal abnormalities. Deletion or monosomy of chromosome 7 was the most frequent abnormality; in 17 cases (48% of those with clonal abnormalities) we found whole chromosome loss or, in one case partial loss due to translocation. In addition, the twins with CMML had constitutional 7;16 translocations, although no acquired changes were found in their marrow cells.

The clones in six cases (17%) contained extra copies of chromosome 8 (in four cases it was the sole abnormality), whereas trisomy 21 and structural abnormalities of chromosome 5 were each found in four cases (11%). In two of the cases with chromosome 5 involvement the abnormalities were interstitial long-arm deletions, whereas two cases with eosinophilia had translocations involving 5q31-33 t(5;12) (q31;q13) and t(1;5)(q22;q33).

Modified classification. We modified the FAB classification by incorporating the categories of JCML and IMo7 using the criteria described above.

Table 2 shows the clinical and laboratory findings in the patients who were reclassified as JCML, IMo7 syndrome, and the remaining patients with CMML who did not have features of these diagnoses. The majority of the patients in these three groups could be readily distinguished from each other and the remaining patients with MDS. The 19 patients with JCML were predominantly male (16 cases) and 11 had a rash at diagnosis; a further child developed the typical rash later in the disease. There were no consistent cytogenetic abnormalities, although two had trisomy 8. Only two patients classified as JCML produced diagnostic problems; case 20 with RA, gross dyserythropoiesis, thrombocytopenia, and an elevated HbF developed a typical rash, and proved resistant to all chemotherapy, whereas case 21 was typical in every way, except that he lacked an absolute monocytosis at the time of diagnosis.

The patients with IMo7 were also predominantly male with morphologic features of RAEB or CMML. Cases 35 and 36 were lost to follow-up. Case 47 had monosomy 7 and has been classified in the group of other CMML because he was 9 years old at diagnosis. However, as symptoms of recurrent infection had been present for many years, he probably represents a case of undiagnosed IMo7. A summary of the expanded classification with numbers of all the other subtypes of MDS is shown in Table 3.

Transformation to AML. Table 3 also shows details of transformation to AML; no patient transformed to lymphoblastic leukemia. Transformation may have been underestimated within this series. Many patients had supportive treatment only and few subsequent investigations, but it was seen in 14 of the 60 patients for whom there was sufficient follow-up information. Transformation occurred almost exclusively in patients with RA, RAEB, RAEBT, or IMo7, almost half of whom developed AML. The rapid clinical deterioration in most cases of JCML was associated with increasing requirement for blood products and debilitation, rather than development of frank AML.

Response to treatment. The patients were followed over a period of 23 years, during which time, treatment was extremely variable, ranging from supportive care only to bone marrow transplantation using a matched unrelated donor (MUD).

Table 4 shows brief details of the treatments received according to the modified FAB classification. Thirty-one patients received supportive treatment only or oral treatment with mercaptopurine and steroids; eight of these are alive and cytogenetic remission. Three of these subsequently relapsed, but the other four remain in first remission, three after chemotherapy alone and one after additional ABMT; a fifth is alive in second remission after an isolated testicular relapse. Twelve patients received an allogeneic BMT, eight from a histocompatible sibling and four from other donors; five of the 12 survive. None of the four children with JCML who received intensive chemotherapy achieved a remission.
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Table 2. Diagnostic Features in Children With JCML, IMo7, or CMML

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age/Sex at Diagnosis (mo)</th>
<th>Liver</th>
<th>Spleen</th>
<th>Lymph Nodes</th>
<th>Rash</th>
<th>HbF (%)</th>
<th>WBC 10^9/L</th>
<th>Cytogentic</th>
<th>FAB Type</th>
<th>Treatment</th>
<th>Survival (mo)*</th>
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<td>NIC</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>43</td>
<td>9/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>1</td>
<td>17</td>
<td>45,XY, -7</td>
<td>CMML</td>
<td>IC</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>44</td>
<td>7/F</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>2</td>
<td>89.7</td>
<td>45,XX, -7</td>
<td>CMML</td>
<td>IC</td>
<td>120*</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>32/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>11</td>
<td>66.2</td>
<td>45,XY, -7</td>
<td>CMML</td>
<td>IC</td>
<td>13</td>
</tr>
<tr>
<td></td>
<td>46</td>
<td>4/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>4</td>
<td>18.2</td>
<td>45,XY, -7</td>
<td>CMML</td>
<td>IC + ABMT</td>
<td>36*</td>
</tr>
<tr>
<td></td>
<td>9</td>
<td>3/F</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>1</td>
<td>81.3</td>
<td>46,XX</td>
<td>CMML</td>
<td>NIC</td>
<td>77*</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>1.5/F</td>
<td>×</td>
<td>✓</td>
<td>✓</td>
<td>ND</td>
<td>32.2</td>
<td>46,XX</td>
<td>CMML</td>
<td>S</td>
<td>270*</td>
</tr>
<tr>
<td></td>
<td>11</td>
<td>6/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>3</td>
<td>10.8</td>
<td>46,XY, t(7;16)(p10;q10)</td>
<td>CMML</td>
<td>NIC</td>
<td>11*</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>6/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>4</td>
<td>14.1</td>
<td>46,XY, t(7;16)(p10;q10)</td>
<td>CMML</td>
<td>NIC</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>14</td>
<td>6/M</td>
<td>✓</td>
<td>✓</td>
<td></td>
<td>8.6</td>
<td>57.6</td>
<td>47,XY, +8</td>
<td>CMML</td>
<td>NIC</td>
<td>149*</td>
</tr>
<tr>
<td></td>
<td>17</td>
<td>13/M</td>
<td>✓</td>
<td>×</td>
<td>×</td>
<td>3</td>
<td>19.2</td>
<td>47,XY, + r.c.</td>
<td>CMML</td>
<td>None</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>48/F</td>
<td>×</td>
<td>✓</td>
<td>×</td>
<td>0.3</td>
<td>18.8</td>
<td>47,XX, +G</td>
<td>CMML</td>
<td>BMT</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>47</td>
<td>112/M</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>0.5</td>
<td>5.7</td>
<td>45,XY, -7</td>
<td>CMML</td>
<td>None</td>
<td>44*</td>
</tr>
<tr>
<td></td>
<td>48</td>
<td>6/M</td>
<td>✓</td>
<td>✓</td>
<td>×</td>
<td>7</td>
<td>37.9</td>
<td>46,XY</td>
<td>CMML</td>
<td>NIC</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td>49</td>
<td>22/M</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>5</td>
<td>30</td>
<td>46,XY</td>
<td>CMML</td>
<td>S</td>
<td>218*</td>
</tr>
</tbody>
</table>

Abbreviations: S, splenectomy; ✓, present; ×, absent; —, unknown; BMT, allogeneic bone marrow transplant; MUD, matched unrelated donor bone marrow transplant; ABMT, autologous bone marrow transplant; NIC, nonintensive chemotherapy (prednisolone = 6-mercaptopurine); IC, intensive chemotherapy as given for AML; ND, not done.

* Still alive.

Survival. Three of the patients have been lost to follow-up. The overall 5-year survival rate for the remaining 65 was 31.9% (95% CI, 21.7% to 44.1%), but there was considerable variation between subgroups. Analysis of survival according to FAB type showed a significant difference (P = 0.013), but our revised classification produces a more even distribution of patients and is more highly significant (Fig 2) P = 0.0009. The only survivor with JCML is one of the four who had a BMT. Six of 10 children with other CMML survive. The one patient with RARS, omitted from these graphs, died after BMT from a matched unrelated donor.

Prognostic factors. The factors shown to influence prognosis in univariate analysis are listed in Table 5. When all the patients were included in the analysis, sex and age were...
Table 3. Modified Classification of MDS

<table>
<thead>
<tr>
<th>Revised Type</th>
<th>No.</th>
<th>FAB Type</th>
<th>Median Age (mo) (range)</th>
<th>Male/Female Ratio</th>
<th>Transformation to AML (as a proportion of the no. for whom this information is available)</th>
<th>Proportion With Follow-Up Surviving</th>
</tr>
</thead>
<tbody>
<tr>
<td>RA</td>
<td>11</td>
<td>11 RA</td>
<td>90 (1.5-140)</td>
<td>6:5</td>
<td>3/9</td>
<td>6/11</td>
</tr>
<tr>
<td>RARS</td>
<td>1</td>
<td>1 RARS</td>
<td>71</td>
<td>0:1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>RAEB</td>
<td>8</td>
<td>8 RAEB</td>
<td>71 (16-141)</td>
<td>0:1</td>
<td>5/6</td>
<td>2/7</td>
</tr>
<tr>
<td>RAEBT</td>
<td>4</td>
<td>4 RAEBT</td>
<td>71 (36-131)</td>
<td>0:1</td>
<td>5/6</td>
<td>2/7</td>
</tr>
<tr>
<td>JCML</td>
<td>19</td>
<td>1 RAEB</td>
<td>36 (5-78)</td>
<td>0:1</td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 RAEB</td>
<td></td>
<td></td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17 CMML</td>
<td></td>
<td></td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>IMo7</td>
<td>12</td>
<td>4 RAEB</td>
<td>10 (4-42)</td>
<td>11:1</td>
<td>4/10</td>
<td>4/10</td>
</tr>
<tr>
<td></td>
<td></td>
<td>8 CMML</td>
<td></td>
<td></td>
<td>0/1</td>
<td>0/1</td>
</tr>
<tr>
<td>CMML</td>
<td>10</td>
<td>10 CMML</td>
<td>6 (1.6-113)</td>
<td>7:3</td>
<td>0/10</td>
<td>6/10</td>
</tr>
<tr>
<td>EOS</td>
<td>3</td>
<td>3 Eosinophilia</td>
<td>44 (6-99)</td>
<td>1:2</td>
<td>0/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Total</td>
<td>68</td>
<td>68</td>
<td></td>
<td></td>
<td>48:22</td>
<td>14/60</td>
</tr>
</tbody>
</table>

not of prognostic significance. However, within the FAB type, CMML, children aged less than 2 years have significantly better survival (chi-squared = 6.69 on 1 df, P = .01). A low platelet count and elevated HbF at diagnosis were both associated with a poor prognosis. The children classed by us as having JCML had a worse survival rate than those with IMo7 (chi-squared = 8.28 with 1 df, P = .004). When patients from all revised FAB types were considered together, again those with JCML had significantly shorter survivals than those with IMo7 or CMML (chi-squared = 15.52 with 1 df, P = .00008).

The proportion of blasts in blood or marrow was not significant nor was the presence of ALIP in the bone marrow trephine, but the number of cases studied was small.

Stratification by cytogenetic complexity score showed a significant difference between a score of one and two and all the patients with complex abnormalities have died.

The Bournemouth score² (based on diagnostic values for hemoglobin, neutrophil count, platelet count, and percentage bone marrow blasts), could be assigned to 62 of the 65 patients with follow-up data. Seventeen of the patients had a score of two and 28 scored three, with no survival difference between these two groups. As this constituted over two-thirds of the patients, the score proved a poor method of discrimination. The more recently described modified Bournemouth system⁴ adds cytogenetic score, other cytopenias, and ALIP, but in our series, these latter two variables did not have significant prognostic value and so the system was not helpful.

In view of the above findings, we developed a pediatric scoring system (HbF-Platelets-Cytogenetics [FPC]), based on objective criteria that could be measured at diagnosis. Each of the following factors scored one point if present at diagnosis: platelets \( \leq 40 \times 10^9/\text{L} \), cytogenetic complexity score of two, and HbF more than 10%. Those patients who scored two or more were compared with those scoring 0 or 1, with the highly significant result shown in Fig 3. The FPC score, as seen in Table 5, and Fig 3 produces more

Table 4. Response to Treatment by Modified Classification

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Supportive or NIC Only</th>
<th>Splenectomy</th>
<th>IC ( \geq ) ABMT</th>
<th>BMT (alive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDS Type</td>
<td>No. Evaluable</td>
<td>Total</td>
<td>Total alive</td>
<td>Total Remission</td>
</tr>
<tr>
<td>RA</td>
<td>11</td>
<td>4</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>RARS</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAEB</td>
<td>7*</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>RAEBT</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>JCML</td>
<td>19</td>
<td>11</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IMo7</td>
<td>10†</td>
<td>4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>CMML</td>
<td>10</td>
<td>7</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>EOS</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>31</td>
<td>8</td>
<td>3</td>
</tr>
</tbody>
</table>

Abbreviations: NIC, nonintensive chemotherapy; IC, intensive chemotherapy; ABMT, autologous bone marrow transplant; BMT, allogeneic bone marrow transplant.

* One patient lost to follow-up.
† Two patients lost to follow-up.
‡ Two patients had interferon.
significant discrimination than morphologic subtypes or adult scoring systems. The score retained prognostic significance after the exclusion of patients with JCML and RAEBT ($P = .0002$).

**DISCUSSION**

Both myelodysplasia and myeloproliferative diseases are uncommon in childhood and, perhaps because small series of patients are the norm, the nomenclature has remained confusing. The traditional hematologic separation of myelodysplasia and myeloproliferative disorders is one that was not made in early pediatric references. There is particular confusion over the term Juvenile Chronic Myeloid Leukemia, which was coined originally to distinguish it from Ph-positive CGL and is somewhat of a misnomer because these patients have the blood and bone marrow appearances of myelodysplasia, usually that of CMML. Other nonleukemic myeloproliferative diseases are exceptionally rare, and we encountered no cases of polycythemia rubra vera or essential thrombocytopenia.

The absolute incidence of MDS in childhood is unknown and a true estimate must await prospective, population-based studies. The reported incidence rates, hitherto based on relatively small populations, have suggested that MDS comprises 1.1% to 8.7% of hematologic malignancies in childhood.

This series of children comprises the largest group of pediatric MDS reported to date, and has the advantage that cytogenetic analysis has been performed in most cases. We have identified a number of problems with definition and classification, using the methods designed for adult MDS, and have attempted to resolve these by modification of the FAB system and by the use of a pediatric prognostic score.

Nineteen of the patients had other clinical abnormalities

**Table 5. Analysis of Prognostic Factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>Group</th>
<th>No.</th>
<th>Ratio of Observed to Expected Deaths</th>
<th>$P$ Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelets</td>
<td>0-40 $\times 10^9$/L</td>
<td>34</td>
<td>1.48</td>
<td>.006</td>
</tr>
<tr>
<td></td>
<td>&gt;40 $\times 10^9$/L</td>
<td>30</td>
<td>0.64</td>
<td>.006</td>
</tr>
<tr>
<td>HbF</td>
<td>0-10%</td>
<td>23</td>
<td>2.02</td>
<td>.00009</td>
</tr>
<tr>
<td></td>
<td>&gt;10%</td>
<td>35</td>
<td>0.64</td>
<td>.006</td>
</tr>
<tr>
<td>FAB</td>
<td>RA</td>
<td>12</td>
<td>0.65</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>RAEB</td>
<td>10</td>
<td>0.82</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>RAEBT</td>
<td>4</td>
<td>3.64</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>CMML</td>
<td>35</td>
<td>1.17</td>
<td>.013</td>
</tr>
<tr>
<td>Modified FAB classification</td>
<td>RA</td>
<td>11</td>
<td>0.49</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>RAEB or RAEBT</td>
<td>11</td>
<td>1.32</td>
<td>.013</td>
</tr>
<tr>
<td></td>
<td>JCML</td>
<td>19</td>
<td>2.53</td>
<td>.00009</td>
</tr>
<tr>
<td></td>
<td>other CMML</td>
<td>10</td>
<td>0.43</td>
<td>.00009</td>
</tr>
<tr>
<td></td>
<td>iMo7</td>
<td>10</td>
<td>0.7</td>
<td>.00009</td>
</tr>
<tr>
<td>Cytogenetic complexity score</td>
<td>1</td>
<td>25</td>
<td>0.72</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>10</td>
<td>2.01</td>
<td>.01</td>
</tr>
<tr>
<td>Pediatric FPC score (see text)</td>
<td>0</td>
<td>19</td>
<td>0.35</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>15</td>
<td>1.19</td>
<td>.01</td>
</tr>
<tr>
<td></td>
<td>2, 3</td>
<td>19</td>
<td>2.33</td>
<td>.01</td>
</tr>
</tbody>
</table>

* Total with follow-up = 65.
† Heterogeneity or trend ($\chi^2$).
or a family history of MDS. There are a number of well-
recognized genetic disorders, which predispose to
leukemia and MDS, and several of these were represented, notably
Shwachman’s syndrome,\textsuperscript{23} familial platelet storage pool
defects,\textsuperscript{24} and NF. Patients with NF appear to have a distinct
risk of JCML, and probably IMo7.\textsuperscript{27} Both IMo7 and JCML
were far more common in boys as has been noted pre-
viously.\textsuperscript{3,24} However, none of the 12 children classified as
IMo7 had an affected family member as described in other
reports.\textsuperscript{20,30} Three of our patients had constitutional chromo-
somal abnormalities, although it is unclear whether these
played a part in the evolution of the disease process.

It was possible to assign FAB classification to all patients
in the study, except the three children with eosinophilia. The
major limitation of the system was the finding that a large
number of children had CMML (reflecting the high fre-
quency of monocytosis in children with these disorders), and
that their prognoses and responses to treatment were very
variable; some dying within months and others experiencing
long-term survival with minimal treatment. The patients re-
classified as JCML tended to be older, to have an extremely
poor prognosis, and were unresponsive to any form of che-
motherapy. Our findings confirm a previous report\textsuperscript{4} from the
Hopital St Louis, which preceded the acceptance of the FAB
system, and described the clinical variability and outcome
in a group of children with morphologic CMML. They
found, like us, that older children with CMML had a worse
prognosis; however, we were unable to show any relation
between blast count and prognosis.

The distinction between JCML and IMo7, our other addi-
tional subgroup, is not always straightforward and difficul-
ties in discriminating between the two disorders have been
emphasized previously.\textsuperscript{5,6} In fact, our patients could be as-
signed fairly easily and this distinction was a helpful one,
with a significant difference in outcome between the two
groups. Monosomy 7 is a common finding in both MDS and
AML, and in the latter is associated with a poor response to
treatment.\textsuperscript{7} It was only children we classified as having IMo7
syndrome who responded to intensive chemotherapy.

The respective frequency of the various subtypes of MDS
in children is unknown. Pooled data from the 1987 MIC
workshop\textsuperscript{8} suggest that in adults RA, RARS, and RAEB
each constitute around a quarter of cases, although RA is
possibly slightly more common. The dominance of CMML
in our cases may reflect referral bias, because this subtype
has been in a minority in some recent series.\textsuperscript{5,7} However, it
is also possible that predominance in some series of patients
with RAEB and RAEBT may reflect the bias of a leukemia
referral pattern because careful examination of children re-
ferred with suspected AML may show some to have features
of MDS; as many as 17% of cases in one series.\textsuperscript{34} It seems
likely that the more indolent forms of RA and RARS may
be underestimated in pediatric practice because they might
not necessarily be referred or may be diagnosed as congenital
dyserythropoietic or sideroblastic anemias.

The risk of transformation to AML in adults with MDS
is reported as 15% to 64%.\textsuperscript{2,3} Although probably underesti-
mated, the development of AML in our series (25%) is in
keeping with this range.

Cytogenetic analysis of the bone marrow proved invaluable
in assessment and had been performed in 63 of our
patients. As in adult patients with MDS, the most common
chromosome abnormalities involved chromosomes 5, 7, and
and 8. Two patients with eosinophilia had translocations involving 5q31-33.\textsuperscript{20,21} The genes encoding interleukin (IL)-3, IL-4,
IL-5, and granulocyte-macrophage colony-stimulating factor
(GM-CSF) form a cluster in this region on chromosome 5,
and there is now good evidence that IL-5 is the major cyto-
kine involved in the production of specific eosinophilia.\textsuperscript{35} It
is possible that in these two cases, eosinophil overproduction
may be the result of inappropriate gene activation caused
by the translocations. There is evidence in adults that the
chromosomal changes in MDS are not the initiating patho-
genic event, especially as many appear late in the clinical
course.\textsuperscript{36} The fact that increased cytogenetic complexity was
associated with shorter survival probably reflects the expan-
sion of a genetically unstable clone in these cases.

Only 7 of 19 children had some response to intensive
chemotherapy of the type used in AML. It appears that chil-
dren with MDS, like adults,\textsuperscript{5,3,30,34} respond poorly to intensive
chemotherapy or succumb to infection during prolonged pe-
riods of marrow failure. These problems may be related
to paucity of normal marrow precursors or expression of
multidrug resistance, which has been reported in 40% of
cases of de novo MDS in adults.\textsuperscript{36} Bone marrow transplanta-
tion appears to be the most effective form of treatment for
MDS in childhood\textsuperscript{37,39} and five of our eight patients who had
BMT from a histocompatible sibling survive. The optimum
timing, the type of preparative regimen, and the role of pre-
transplant chemotherapy remain to be defined. The role of
BMT from a matched unrelated donor\textsuperscript{40} is, as yet, unclear
but will become apparent in the next few years.

With the exception of one of the children, a boy with
eosinophilic MDS who received α-interferon that resulted
in some improvement,\textsuperscript{41} no patients received other growth
factors or cytokine therapy. There is clearly a need for sys-
tematic evaluation of this type of therapy in pediatric, as in
adult myelodysplasia.

The examination of prognostic factors in this group of
patients, seen over a long period of time and given a variety
of treatments, must clearly be interpreted with extreme cau-
tion. It was undertaken to act as a base for future prospective
surveys and to provide some guidance in identifying a very
high-risk group of patients who might, for example, benefit
from early consideration of BMT from a matched unrelated
donor. Conversely, intensive treatment may not be appro-
priate in patients with no unfavorable prognostic factors,
particularly young children with CMML.

The assignment of an FAB type was of some value, but
our modification of this was more useful. There was no

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evidence that a dominance of blasts in either the blood or the bone marrow had a significant effect on survival, and sex and age, were other than in the context of CMML, were of no prognostic significance. A number of scoring systems have been described to predict prognosis in adult MDS. The Bournemouth scoring system3,4 had poor discriminatory power, and we were unable to use the Dusseldorf system5 because one of the components, lactate dehydrogenase (LDH), was not measured in our patients.

Our simple pediatric FPC score based on HbF, the diagnostic platelet count, and cytogenetic score (a straightforward cytogenetic complexity score that does not need to be modified according to the chromosome involved as in the modified Bournemouth system) is completely objective and does not depend on precise assignment of the FAB or modified FAB type. It provided a high level of discrimination between groups, and would clearly identify most patients at risk of early death.

In conclusion, we have shown that a large proportion of children with MDS have associated abnormalities, a finding that must have implications for investigations of pathogenesis. The FAB classification of MDS is of limited value in pediatric myelodysplasia, though with some modifications to admit clinical and cytogenetic information and to incorporate eosinophilic cases, it appears to work well. We have devised a simple scoring system that appears to discriminate between risk groups in pediatric patients—the adult scoring systems did not. Both classification and scoring systems need to be assessed prospectively on large numbers of patients. Population-based studies are needed to determine the true incidence of pediatric MDS and the proportion of the various subtypes. Such studies are now being undertaken.

ACKNOWLEDGMENT

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Pediatric myelodysplasia: a study of 68 children and a new prognostic scoring system

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