Prospective Study of 90 Children Requiring Treatment for Juvenile Myelomonocytic Leukemia or Myelodysplastic Syndrome: A Report From the Children’s Cancer Group

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Purpose: We report the first large prospective study of children with myelodysplastic syndrome (MDS) and juvenile myelomonocytic leukemia (JMML) treated in a uniform fashion on Children’s Cancer Group protocol 2891.

Patients and Methods: Ninety children with JMML, various forms of MDS, or acute myeloid leukemia (AML) with antecedent MDS were treated with a five-drug induction regimen (standard or intensive timing). Patients achieving remission were allocated to autologous BMT and aggressive nonmyeloablative chemotherapy. Results were compared with patients with de novo AML.

Results: Patients with JMML and refractory anemia (RA) or RA-excess blasts (RAEB) exhibited high induction failure rates and overall remission of 58% and 48%, respectively. Remission rates for patients with RAEB in transformation (RAEB-T) (69%) or antecedent MDS (81%) were similar to de novo AML (77%). Actuarial survival rates at 6 years were as follows: JMML, 31% ± 26%; RA and RAEB, 29% ± 16%; RAEB-T, 30% ± 18%; antecedent MDS, 50% ± 25%; and de novo AML, 45% ± 3%. For patients achieving remission, long-term survivors were found in those receiving either autologous BMT or chemotherapy. The presence of monosomy 7 had no additional adverse effect on MDS and JMML.

Conclusion: Childhood subtypes of MDS and JMML represent distinct entities with distinct clinical outcomes. Children with a history of MDS who present with AML do well with AML-type therapy. Patients with RA or RAEB respond poorly to AML induction therapy. The optimum treatment for JMML remains unknown.


The myelodysplastic syndromes (MDS) represent a heterogeneous group of disorders of hematopoiesis leading to variable degrees of pancytopenia and often acute myeloid leukemia (AML). In adults, MDS has been classified by the French-American-British (FAB) group into several distinct categories, with abnormal myelopoiesis associated with dysplastic blood and marrow a common feature. MDS subtypes include refractory anemia (RA), RA with ringed sideroblasts (RARS), RA with excess blasts (RAEB), RAEB in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML). The FAB MDS classification for adults does not adequately address all syndromes that occur in children. RA and RARS are rare in children, whereas other syndromes are more common, including the monosomy 7 syndrome and juvenile myelomonocytic leukemia (JMML) (formerly juvenile chronic myeloid leukemia). The latter shares some characteristics with adult CMML and is not a true MDS.

The childhood and adult myelodysplastic syndromes, as well as JMML, are subject to ongoing controversies as to optimum diagnostic classification and treatment. Many have argued that patients with MDS, especially adults, have fragile myelopoiesis that cannot withstand aggressive myelosuppressive chemotherapy as traditionally used in AML or that prognosis with such an approach is poor. We and other investigators have previously argued that, on the contrary, MDS in children often represents a preleukemic condition that, like overt leukemia, will respond to aggressive myelosuppressive therapy similar to that used in AML, with recovery of normal myelopoiesis if successful. The role and timing of bone marrow transplantation (BMT) have been debated. Finally, the role of monosomy 7 in predicting the prognosis of patients with MDS has not been clarified. Monosomy 7 is a poor prognostic factor in childhood AML. It has been proposed that this is an entity distinct from other childhood MDS, and there is a high incidence of monosomy 7 in patients with MDS.
We herein present data on 90 consecutive patients with MDS or JMML entered prospectively onto a Children’s Cancer Group (CCG) protocol for children with newly diagnosed AML.

PATIENTS AND METHODS

CCG protocol 2891 was initiated in October 1989 for the treatment of children with newly diagnosed AML, MDS, or JMML and closed in April 1995. Patients with MDS and JMML were eligible for treatment if deemed to require intervention by their treating physician, usually for severe neutropenia or thrombocytopenia. No attempt was made to document the number of patients diagnosed with MDS or JMML who did not require treatment at the time of diagnosis. Patients with Fanconi anemia were not eligible for this study.

Details of therapy have been previously published.12 All patients with AML, MDS, and JMML, were randomized to a timing-intensive induction and piloted in CCG-286116 or to a more standard timing approach using identical drugs and doses, called DCTER (dexamethasone, cytarabine, 6-thioguanine, etoposide, and rubidomycin [daunomycin]). Patients who achieved remission after two courses (four cycles) and who had family-matched donors were eligible for allogeneic BMT with busulfan and cyclophosphamide myeloablation. All other patients were randomized between autologous BMT using 4-hydroperoxycyclophosphamide–purged marrows, as in CCG-2861, and an aggressive postremission approach using several cycles of nonablative marrow therapy, including intensively timed high-dose cytarabine.15,14 Patients with AML receiving intensive timing exhibit a markedly superior outcome compared with those receiving standard-induction timing.15 and patients allocated to allogeneic BMT had superior results over chemotherapy or autologous BMT in the postremission phase.15

All patients enrolled onto CCG-2891 had institutional FAB and other pediatric MDS types noted. Final consensus MDS subtypes were decided by a central study committee, which considered review of clinical (W.G.W.), morphologic (D.R.B.), and cytogenetic (D.C.A.) material. Central review of MDS morphology was used when available (75% of the time); otherwise, institutional morphologic classification was used. Strict adherence to FAB definitions was practiced. The diagnosis of JMML was made when morphology suggested CMML and patients had increased fetal hemoglobin levels compared with age-based controls. Patients presenting with AML and a previous history of MDS had MDS marrow examinations performed by the local institution, with central review when available.

Data on patients enrolled onto CCG-2891 were collected at individual institutions and entered into the Children’s Cancer Group database in Arcadia, CA. Data included various clinical and laboratory characteristics at the time of diagnosis, treatment received, complications noted, various treatment endpoints, such as relapses and sites, major toxic events, including death, and time of last follow-up. Remission, as in AML, was defined as less than 5% marrow blasts, with recovery of all three myelopoietic lineages and peripheral-blood counts.

Statistical Considerations

Analyses of data obtained in this study through August 2000 were performed with the use of several standard methods. Results were calculated as of the day of last contact, with a cutoff of February 11, 2000, hence a minimum follow-up of 5 years. Accrual goals for this study were determined for patients with AML before study initiation. For the postremission randomization, patients were stratified according to induction regimen received.

Differences in survival and event-free survival from the time of study and in survival and disease-free survival from the end of induction were tested for significance using the log-rank statistic.16 Patients lost to follow-up were censored at their last known point during the study. Survival curves were estimated by the method of Kaplan and Meier,17 and confidence intervals were calculated using Greenwood’s formula.18 The significance of observed differences in proportions was tested using the $\chi^2$ statistic and Fisher’s exact test when appropriate for small samples. All reported comparisons are based on regimens to which patients were allocated or randomized (intent to treat). Comparisons were also made for regimens actually received, when appropriate for small numbers in some subsets of MDS.

There were only two patients diagnosed with RA on CCG-2891. One died during induction; the other withdrew before remission status could be determined, underwent an alternative transplant, and is a long-term survivor. These two patients are included in all analyses with the 33 patients with RAEB. For analyses examining the effect of monosomy 7 on outcome, a subset of the CCG-2891 data set representing all patients with adequate karyotypes (53%) was used. Overall, CCG-2891 results do not vary between patients with and without cytogenetic data.12,15

RESULTS

Patient Characteristics and Pathology Review

During the 5.5-year period of the study, 1,096 patients were enrolled onto and eligible for CCG-2891. For the purposes of this report, we have excluded patients with Down’s syndrome ($n = 104$), granulocytic sarcoma with no evidence of bone marrow involvement ($n = 8$), and AML as a second malignant neoplasm ($n = 23$). Of the 961 remaining patients, 871 had AML, 16 had a history of MDS but presented with overt AML, and 74 had various forms of MDS or JMML (referred to as MDS/JMML throughout the text). They included the following: JMML, 13; RA, 2; RAEB, 33; and RAEB-T, 26. Hence, 9.4% of all patients either presented with MDS/JMML or had a history of MDS before enrollment.

Table 1 compares institutional MDS and JMML diagnoses with consensus subgroup classification. Overall, the sensitivity of institutional diagnoses distinguishing MDS/JMML from AML compared with the consensus classification was 63 (85%) of 74. Within MDS/JMML subtypes, institutional concordance with the consensus classification was 47 (75%) of 63. Only 11 of 887 consensus AML cases were originally called MDS by institution pathologists.

Patient characteristics of the children presenting with MDS or JMML are given in Table 2, with comparisons to AML patients ($n = 887$) enrolled onto CCG-2891. MDS patients as a group had lower leukocyte counts (WBCs) than patients who presented with de novo AML. Similarly, the incidence of abnormal CSF cytology was significantly less in patients with MDS. Both MDS and JMML patients had a reduction in common structural cytogenetic abnormalities found in patients with AML, such as t(8;21), 11q23 abnor-
malities, and inv16q. On the other hand, there was a significantly higher incidence of monosomy 7 in patients with MDS. Only one patient (10%) with JMML had monosomy 7. Monosomy 5, a common cytogenetic abnormality in adults with MDS, was seen in one child (2%) with RAEB. Patients with JMML were younger, had more extramedullary disease, and exhibited a higher percentage of normal cytogenetics compared with both AML and MDS patients.

AML patients with a history of MDS had remarkably similar clinical characteristics to those with de novo AML, with two exceptions. Patients with a history of MDS had lower WBCs (10,100/L v 21,700/L, P < .02) and less extramedullary disease or marked organomegaly (0% v 30%, P = .05).

Patient characteristics among the various MDS subtypes were analyzed. The major notable finding was a much higher proportion of monosomy 7 among the RA (two of two) and RAEB (eight of 16) patients compared with the other MDS subtypes (data otherwise not shown).

Induction Outcome

Table 3 demonstrates the induction outcome and time to completion for patients with MDS/JMML, patients with a history of MDS who presented with AML, and those with de novo AML. A steady improvement in the induction success rate was noted from RA/RAEB to RAEB-T to AML. Inability to achieve remission, while remaining alive, was markedly increased in patients with JMML, RA/RAEB, and RAEB-T. Overall, 32% of patients with MDS/JMML had resistant leukemia compared with 16% patients with AML (P = .002). No overall differences were seen in the toxic death rates among the various groups, where the overwhelming cause of death was infection. Interestingly, there was no suggestion that the children with MDS/JMML required more time to complete induction secondary to prolonged blood counts. No difference in induction outcome was seen between those with and without a previous history of MDS but treated in the AML phase.

Similar to patients with de novo AML previously reported,12 patients with RA/RAEB and RAEB-T combined had a lower induction failure rate with intensive-timing DCTER compared with standard-timing DCTER, 22% v 50% (P = .03). Overall, 64% of combined RA/RAEB and RAEB-T patients treated with intensive-timing DCTER achieved remission compared with 45% treated with standard-timing DCTER (P = .17).

### Table 1. Comparison of Institutional and Consensus AML and MDS Subtypes

<table>
<thead>
<tr>
<th>Consensus Diagnosis</th>
<th>JMML</th>
<th>RA/RAEB</th>
<th>RAEB-T</th>
<th>MDS*</th>
<th>AML†</th>
<th>Total</th>
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</thead>
<tbody>
<tr>
<td>JMML</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>13</td>
</tr>
<tr>
<td>RA/RAEB</td>
<td>0</td>
<td>26†</td>
<td>2</td>
<td>1</td>
<td>6</td>
<td>35</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>0</td>
<td>4</td>
<td>16</td>
<td>1</td>
<td>5</td>
<td>26</td>
</tr>
<tr>
<td>AML†</td>
<td>1</td>
<td>3</td>
<td>6</td>
<td>1</td>
<td>876</td>
<td>887</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>34</td>
<td>25</td>
<td>3</td>
<td>887</td>
<td>961</td>
</tr>
</tbody>
</table>

*Not otherwise specified, other.
†Includes patients with history of MDS who entered study with AML.
‡Includes six consensus RAEB patients classified as RA by institutions.

### Table 2. Characteristics of Patients: MDS/JMML Versus AML

<table>
<thead>
<tr>
<th></th>
<th>MDS (n = 61)</th>
<th>P</th>
<th>JMML (n = 13)</th>
<th>P</th>
<th>AML (n = 887)</th>
<th>P Compared With MDS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years</td>
<td>6.8</td>
<td>.007</td>
<td>3.4</td>
<td>.002</td>
<td>7.8</td>
<td>.43</td>
</tr>
<tr>
<td>Median WBC count, μL</td>
<td>6,900</td>
<td>.0002</td>
<td>25,900</td>
<td>.39</td>
<td>21,000</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Extramedullary disease, %</td>
<td>13</td>
<td>&lt; .0001</td>
<td>77</td>
<td>.001</td>
<td>29</td>
<td>.007</td>
</tr>
<tr>
<td>(+) Blasts in CSF, %</td>
<td>7</td>
<td>.99</td>
<td>0</td>
<td>.08</td>
<td>21</td>
<td>.007</td>
</tr>
<tr>
<td>Normal cytogenetics,* %</td>
<td>21</td>
<td>.001</td>
<td>80</td>
<td>&lt; .0001</td>
<td>24</td>
<td>83</td>
</tr>
<tr>
<td>t(8;21),* %</td>
<td>3</td>
<td>.99</td>
<td>0</td>
<td>.61</td>
<td>11</td>
<td>24</td>
</tr>
<tr>
<td>11q23 abnormalities,* %</td>
<td>3</td>
<td>.99</td>
<td>0</td>
<td>.38</td>
<td>16</td>
<td>.04</td>
</tr>
<tr>
<td>inv16q,* %</td>
<td>0</td>
<td>.99</td>
<td>0</td>
<td>.99</td>
<td>8</td>
<td>.16</td>
</tr>
<tr>
<td>−7*</td>
<td>36†</td>
<td>.24</td>
<td>10</td>
<td>.34</td>
<td>4</td>
<td>&lt; .0001</td>
</tr>
</tbody>
</table>

NOTE. Data are expressed as percentages, except for age (in years) and WBC count (μL).
*Based on the 53% of CCG-2891 patients with adequate, centrally reviewed cytogenetics.
†56% in RA and RAEB.
Overall Outcome

Overall survival at 6 years was 29% ± 12% (95% confidence intervals) for patients with MDS and 31% ± 26% for those with JMML treated on CCG-2891. These outcomes were worse than for those with antecedent MDS and treated in the AML phase (50% ± 25%) or those with de novo AML (45% ± 3%) (Fig 1). Nonsignificant differences in the survival at 6 years from the beginning of the study were seen between patients with JMML (31% ± 26%), RA/RAEB (29% ± 16%), or RAEB-T (30% ± 18%) (Fig 2 and Table 4). Of the MDS subtypes, only patients with RA/RAEB had a significantly worse event-free survival and survival compared with patients with de novo AML (Table 4), probably because of small patient numbers in the subsets.

Effect of Postremission Therapy on Outcome

Forty patients with MDS/JMML who achieved remission were eligible for allocation to allogeneic BMT or randomization between autologous BMT and intensive chemotherapy. Results are given in both Figure 3, in which the three postremission regimens are compared in an intent-to-treat analysis combining MDS and JMML, and Table 5, which gives actual regimen-received outcome data for three subtypes. Overall compliance for MDS/JMML patients with the allocated regimens was 73%, despite some "noncompliers" who relapsed before they could begin their postremission regimen. Patients eligible for allogeneic BMT (n = 6) seem to have a nonsignificant advantage survival (83% ± 30%) at 5 years over intensive chemotherapy patients (n = 13, 52% ± 29%) and autologous BMT patients (n = 9, 22% ± 28%) (P = .07 overall and P = .18 comparing allogeneic BMT to the other two regimens combined), with small numbers in all regimens. Six (38%) of 16 patients who received postremission chemotherapy are long-term disease-free survivors. However, several patients who received no additional therapy or alternative BMTs (eg, matched unrelated donors) are also disease-free (Table 5).

Monosomy 7 as a Potential Confounding Variable

We examined the role of monosomy 7 in predicting the prognosis of patients with MDS and JMML. In this study, 13 (30%) of 43 patients with MDS/JMML with centrally reviewed karyotypes exhibited monosomy 7, compared with only 3% of 465 patients with de novo AML (P < .0001). Only three AML patients with a history of MDS had cytogenetic data, precluding any comparisons to the other

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Table 3. Induction Outcome*

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Time to Complete 4 Induction Cycles (days)</th>
<th>Remission (%)</th>
<th>Resistant Leukemia (%)</th>
<th>Death (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMML</td>
<td>12</td>
<td>77</td>
<td>58</td>
<td>42</td>
<td>0</td>
</tr>
<tr>
<td>RA/RAEB</td>
<td>31</td>
<td>119</td>
<td>48</td>
<td>35</td>
<td>16</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>26</td>
<td>116</td>
<td>69</td>
<td>27</td>
<td>4</td>
</tr>
<tr>
<td>MDS—AML</td>
<td>16</td>
<td>107</td>
<td>81</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td>De novo AML</td>
<td>836</td>
<td>117</td>
<td>77</td>
<td>16</td>
<td>7</td>
</tr>
</tbody>
</table>

*Excludes five patients with JMML or MDS who withdrew alive during induction therapy without remission status determined.
groups. Fifty percent of MDS/JMML patients with monosomy 7 and available data achieved remission, with 30% not maintaining remission and 20% dying. However, this was not different from the overall induction success rate for MDS/JMML (see above; \( P/H_{11005} .42 \) v MDS/JMML patients without monosomy 7). Of those with cytogenetic data, monosomy 7 patients took a median of 113 days to complete the four induction cycles compared with 119 days for the non–monosomy 7 patients \( (P/H_{11005} .39) \). Similarly, event-free survival and survival from on-study for the monosomy 7 patients with MDS/JMML \( (38\% /H_{11006} 27\% \text{ and } 54\% /H_{11006} 28\% \text{ at } 6 \text{ years, respectively}) \) was not statistically different from all other MDS/JMML patients with adequate cytogenetics \( (30\% /H_{11006} 17\% \text{ [} P/H_{11005} .89\text{] and } 30\% /H_{11006} 17\% \text{ [} P/H_{11005} .38\text{], respectively}) \). Hence, although there was a high percentage of monosomy 7 patients in the MDS group, and the MDS group as a whole fared worse than patients with AML, the non–monosomy 7 MDS patients had an outcome similar to those with monosomy 7.

In contrast, the outcome of monosomy 7 patients with AML was significantly worse than for other patients on CCG-2891. Only eight (53%) of 15 monosomy 7 patients achieved remission compared with 78% of the total group \( (P = .03) \). Similarly, overall event-free survival was significantly worse for the monosomy 7 AML patients \( (19\% /H_{11006} 20\% \text{ at } 6 \text{ years v } 39\% /H_{11006} 5\% \text{ for non–monosomy 7 AML patients, } P = .01) \). Survival did not differ significantly \( (47\% /H_{11006} 26\% \text{ v } 46\% /H_{11006} 5\% \text{, } P = .66) \) because of a relatively high salvage rate in monosomy 7 patients, including use of alternative-donor transplants. From the data, it also appears that monosomy 7 AML patients did worse than their MDS counterparts (see above).

**DISCUSSION**

CCG-2891 represents the first large, prospective study of children with MDS and JMML requiring therapy. The patients with MDS/JMML were treated in an identical fashion to those with AML, using current therapy when the study began in 1989. Almost 10% of all patients enrolled had either MDS/JMML or a history of MDS at the time of entry. Patients diagnosed with MDS/JMML not requiring intervention are not included. Hence, this spectrum of myeloid disease is more frequent than many of the discrete AML subtypes seen by CCG, such as M6 or M7.

MDS is quite heterogeneous in children. Furthermore, central consensus review demonstrated that there is some variability among institutions in assigning patients to various MDS subtypes and JMML, with overall concordance of 75%. We believe that central review of the morphologic, cytogenetic, and clinical data was important in our ability to accurately assign patients to the various subtypes and subsequently make valid comparisons. Of these diseases, JMML was most different from MDS, presenting at a much earlier age.

### Table 4. Overall Event-Free Survival and Survival at 6 Years From Diagnosis Comparing MDS, JMML, and AML Patients

<table>
<thead>
<tr>
<th>Disease</th>
<th>No.</th>
<th>EFS (%)</th>
<th>Survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JMML</td>
<td>13</td>
<td>31 ± 26*</td>
<td>31 ± 26*</td>
</tr>
<tr>
<td>RA/RAEB</td>
<td>35</td>
<td>20 ± 14†</td>
<td>29 ± 16‡</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>26</td>
<td>26 ± 18</td>
<td>30 ± 18</td>
</tr>
<tr>
<td>MDS—AML</td>
<td>16</td>
<td>38 ± 24</td>
<td>50 ± 25</td>
</tr>
<tr>
<td>De novo AML</td>
<td>871</td>
<td>38 ± 3</td>
<td>45 ± 3</td>
</tr>
</tbody>
</table>

*\( P = .12\) compared with AML.
†\( P = .0002\) compared with AML.
‡\( P = .03\) compared with AML.

### Table 5. Postremission Outcome for JMML and MDS Subgroups

<table>
<thead>
<tr>
<th>Total DFS</th>
<th>Postremission Therapy Received</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Allogeneic</td>
</tr>
<tr>
<td>JMML</td>
<td>4/7</td>
</tr>
<tr>
<td>RA/RAEB</td>
<td>5/15</td>
</tr>
<tr>
<td>RAEB-T</td>
<td>7/18</td>
</tr>
</tbody>
</table>

Abbreviation: DFS, disease-free survival.
*Three of seven who received alternative BMT are disease-free.
†Two of three who received no additional medication are disease-free.
younger age with higher WBC count and more frequent extramedullary disease. The MDS subtypes in many ways followed a continuum with respect to various characteristics at diagnosis. For example, patients with RA and RAEB had a high rate of monosomy 7, whereas those with RAEB-T and a history of MDS before AML presentation had an intermediate percentage between the other MDS types and patients presenting with de novo AML (Table 2).

The biologic characteristics and clinical outcome of children with MDS, however, suggest that the more adult-type MDS syndromes are not just early AML but may represent distinct diseases.19 As noted in Fig 1 and Table 4, patients with a history of MDS before presenting with AML had induction success rates and overall outcomes similar to patients with de novo AML. On the other hand, the two patients with RA and 33 with RAEB had a much poorer induction success rate, primarily because of inability to reduce the abnormal clone. Limited by the number of patients studied in remission, our results would also suggest that survival after achieving remission is nonsignificantly greater for children with MDS/JMML with matched family donors than those who must rely on chemotherapy or autologous BMT for postremission intensification (Fig 3 and Table 5).

Our data lend strong support to the premise that children with the adult forms of MDS should be treated similarly to adults with the same subtypes, on the basis of recent recommendations.9,10,20,21 Historically, there was initial enthusiasm for considering both children and adults with all subgroups of MDS for allogeneic BMT at diagnosis. Recent data suggest that patients transplanted at diagnosis with RAEB-T, and perhaps RAEB, have a prohibitively high relapse rate.9,10 On the other hand, children and adults transplanted with less than 5% blasts seem to have an excellent outcome with BMT without previous cytoreductive chemotherapy.9,10

Even though this study represents the largest prospective study to date of pediatric MDS/JMML, numbers in various MDS subsets are still small, precluding definitive conclusions. However, on the basis of our data and those of others,9,10,20-24 we believe that the following recommendations can be made for treatment of children with various forms of adult MDS.1

Patients with a history of MDS who present with AML (excluding those with monosomy 7) and many of those with RAEB-T do as well with AML therapy at diagnosis as patients with AML. For example, the one MDS patient with the AML karyotype t(8;21) had RAEB-T. For patients who achieve remission and have no family match, aggressive chemotherapy is acceptable treatment (Fig 3 and Table 5).2 Children with RA/RAEB do not respond to AML induction therapy as well as patients with AML. Because failure rates after BMT are lower in this group when treated at diagnosis, strong consideration should be given for such treatment, especially when a 5/6 or 6/6 matched family donor is available. The optimum therapy for patients with RA/RAEB without matched family donors is unknown. Some of these patients require no therapy for years and have indolent diseases. However, alternative forms of BMT using partially matched related donors,25 matched unrelated donors,26-27 or perhaps cord blood28 should be considered in an exploratory fashion when treatment is required, usually for severe cytopenia.

With respect to the more specific childhood diseases, JMML and monosomy 7 syndrome, recommendations are more difficult. Our data lend no support for the consideration of monosomy 7 as a distinct clinical MDS/JMML entity. In contrast to patients with AML, where monosomy 7 portends a poor prognosis, outcome with or without monosomy 7 was identical in our patients with MDS/JMML. This suggests that the absence of the cytogenetic abnormality may not reflect molecular changes mimicking the loss of critical regions on chromosome 7. Additional interesting molecular work on the role of monosomy 7 in MDS is awaited.29,30 We propose, however, that children with MDS/JMML be classified using a FAB plus JMML schema without regard for cytogenetic status.

The optimum treatment of children with JMML is presently unknown. Few JMML patients exhibit monosomy 7 (in our series, only one of 10 patients studied), and most have normal karyotypes. Our results and those of others9 suggest that aggressive chemotherapy can ameliorate the disease in a substantial minority of patients (Figs 1 and 2 and Tables 3 through 5). Other investigators disagree.30 On the other hand, there may be a role for biologic differentiation agents, such as retinoids.31 No approach leads to optimal results at this time. Large national and international studies should prove critical in determining optimal therapeutic approaches for this uncommon variant of abnormal myelopoiesis.

APPENDIX
Participating Principal Investigators: Children’s Cancer Group

The appendix is available online at www.jco.org.
REFERENCES


