Prognostic Implications of Morphology and Karyotype in Primary Myelodysplastic Syndromes

By Renee H. Jacobs, Michael A. Cornbleet, James W. Vardiman, Richard A. Larson, Michelle M. Le Beau, and Janet D. Rowley

Forty-nine patients with primary myelodysplastic syndromes (MDS) were subclassified according to French-American-British (FAB) Cooperative Group criteria. Eight patients had acquired idiopathic sideroblastic anemia (AISA), ten had chronic myelomonocytic leukemia (CMMoL), 14 had refractory anemia (RA), nine had refractory anemia with excess blasts (RAEB), and five had refractory anemia with excess blasts in transformation (RAEB-T); three patients could not be subclassified. The actuarial median survival for patients with AISA or with RA had not been reached at 60 months of follow-up. The median survival times for patients with CMMoL, RAEB, and RAEB-T were 25, 21, and 16 months, respectively. The percentages of patients with each subtype who developed ANLL were none in AISA, 20% in CMMoL, 7% in RA, 56% in RAEB, and 40% in RAEB-T. Patients with CMMoL had a poor prognosis independent of transformation to acute nonlymphocytic leukemia (ANLL), whereas patients with RAEB and RAEB-T had a high incidence of transformation and short survival times. Clonal chromosomal abnormalities were present in bone marrow cells from 19 patients at the time of diagnosis, and two others developed an abnormal karyotype at the time of leukemic transformation. The most frequent abnormalities, including initial and evolution changes, were trisomy 8 (9 patients), deletion of 5q (4 patients), and deletion of 20q (4 patients). The median survival times were 32 months for patients with an abnormal karyotype, and 48 months for those with a normal karyotype (P = 0.2). Specific chromosomal abnormalities were not associated with particular histologic subtypes; however, a high percentage of patients with RAEB and RAEB-T had an abnormal clone (89% and 80%, respectively). The percentages of patients with clonal abnormalities were 13% for AISA, 20% for CMMoL, and 29% for RA. The MDS transformed to ANLL in 42% of patients with an abnormal karyotype, compared to 10% of those with an initially normal karyotype (P < .01). Among patients with RA, RAEB, and RAEB-T, the risk of leukemic transformation was confined to those with an abnormal karyotype (P < .01). Thus, in the present study, morphology and karyotype combined were the best indicators of outcome in patients with MDS.

© 1986 by Grune & Stratton, Inc.

MATERIALS AND METHODS

The 49 patients described here include all those seen at the University of Chicago Medical Center between 1972 and 1984 with a diagnosis of a primary MDS that could be confirmed by morphologic study of bone marrow specimens. Clinical data were collected

From the Departments of Medicine and Pathology, and The Franklin McLean Memorial Research Institute, University of Chicago.

Supported by the Department of Energy Contract DE-AC02-80EV10360, USPHS Grant CA-16910, and PHS 5-T32 AM07134-10.

Dr Cornbleet is a Hamilton-Fairley Travelling Research Fellow, funded by The Cancer Research Campaign. Dr Le Beau is a Special Fellow of the Leukemia Society of America. Dr Larson is a recipient of a Clinical Oncology Career Development Award from the American Cancer Society.

Submitted Aug 30, 1985; accepted Feb 1, 1986.

Address reprint requests to Renee H. Jacobs, MD, 5841 S. Maryland Ave, Box 420, Chicago, IL 60637.

© 1986 by Grune & Stratton, Inc.

0006-4971/86/6706-0022$03.00/0
by review of each medical record. Patients were followed until death or through April 1985.

Cytogenetic analyses were performed as described previously.13 Initial cytogenetic specimens were obtained before any cytotoxic therapy was given. Chromosome abnormalities were described according to The International System for Human Cytogenetic Nomenclature.14 The criteria proposed by Rowley and Potter were used for the identification of abnormal clones.15

Differential counts of at least 100 white cells were performed on the peripheral blood samples, and of at least 400 nucleated cells on the marrow aspirate smears of each patient. The percentage of ringed sideroblasts was determined from smears or sections stained with a Prussian blue reaction for iron. Dyspoiesis was graded in each cell line as either absent, present, or present and severe. The designation of severe dysplasia was used when more than 50% of the cells in a given series demonstrated dysplastic features, according to the criteria of Juneja et al.15 Abnormal localization of immature precursors (ALIP) was determined according to the criteria of Tricot et al.,16 except that we used paraffin-embedded, 4 to 5 μm thick sections of marrow rather than plastic-embedded marrow specimens. The criteria of the FAB group were used for the diagnosis and classification of each patient.14 If the FAB criteria could not be applied, cases were considered unclassifiable. Acute leukemia was diagnosed when more than 30% type I and type II blasts were present in the marrow.17

Survival was calculated from the time of diagnosis of MDS. Analyses of categorical data were performed with the standard Pearson r x c chi-square statistic. Actuarial survival curves were constructed according to the methods of Berkson and Gage and their significance was tested with a modification of the Wilcoxon method.18,19

RESULTS

Clinical characteristics. The clinical characteristics of the 49 patients with primary MDS are summarized in Table 1. There were eight patients with acquired idiopathic sideroblastic anemia (AISA), 10 with chronic myelomonocytic leukemia (CMMoL), 14 with refractory anemia (RA), nine with refractory anemia with excess blasts (RAEB), and five with refractory anemia with excess blasts in transformation (RAEB-T). All patients with RAEB-T had 20% to 30% blasts in the bone marrow. We were unable to classify three patients according to FAB criteria. In one of these cases, there was severe dysgranulopoiesis and no increase in the number of blasts. In the other two, despite severe trilineage dysplasia, blasts were also not increased in number. Thus, the diagnosis of RA would be inappropriate because the FAB guidelines state that the granulocytic and megakaryocytic series almost always appear normal in that particular disorder.

The patients included 28 males and 21 females, ranging in age from 3 to 85 years; the median age for the entire group was 62 years. Patients with RA were significantly younger than those with the other subtypes of MDS.

The hematologic features at diagnosis are also summarized in Table 1. There was wide variation in the initial hemoglobin concentrations, leukocyte counts, and platelet counts among these patients. The only notable difference in these parameters among the FAB subtypes of MDS was the absence of thrombocytopenia and leukopenia in patients with AISA. Anemia, with its associated symptoms, was the most common hematologic abnormality and was observed in all subtypes of MDS. Only seven patients (14%) had initial hemoglobin values greater than 12 g/dL. At diagnosis, the absolute neutrophil count was less than 1000/μL in only four patients. This was an incidental finding in two patients presenting with anemia. The third had a fever of unknown origin. The fourth patient, who was 3 years old, had an immunodeficiency syndrome characterized by recurrent peripectal abscesses and skin infections. At diagnosis, five patients had life-threatening thrombocytopenia (less than 20,000 platelets/μL). Four of these patients reported easy bruising, but none had significant bleeding.

No patient had palpable lymphadenopathy. A small percentage of patients within each subtype, except AISA, had splenomegaly. However, the degree of splenomegaly was mild, with the spleen ranging in size from being just palpable to extending three centimeters below the costal margin. Hepatomegaly was noted only in three patients with CMMoL, and each of these patients also had splenomegaly.

| Table 1. Patient Characteristics at Diagnosis of Myelodysplastic Syndromes |
|---------------------------------|--------------------|----------------|----------------|--------------|-------------|----------------|
| Number of patients              | AISA               | CMMoL          | RA             | RAEB         | RAEB-T      | Unclassifiable |
| Median age (yr)                 | 68                 | 68             | 49             | 68           | 62          | 54            |
| Median Hgb (g/dL)               | 9.2                | 9.3            | 8.3            | 9.8          | 9.9         | 9.6           |
| (range)                         | (6.2–10.7)         | (7.5–13.5)     | (3.1–13.0)     | (6.4–11.8)   | (8.0–10.5)  | (8.5–10.6)    |
| Median WBC count (× 10^3/μL)    | 4.8                | 31.4           | 6.5            | 4.8          | 7.4         | 4.0           |
| (range)                         | (2.3–6.6)          | (9.3–71.0)     | (2.5–13.8)     | (1.1–7.8)    | (1.1–84.0)  | (3.2–4.8)     |
| Median platelets (× 10^9/μL)    | 312                | 188            | 263            | 50           | 128         | 89            |
| Splenomegaly only (%)           | 0                  | 20             | 7              | 11           | 40          | 0             |
| Hepatosplenomegaly (%)          | 0                  | 30             | 0              | 0            | 0           | 0             |
| Skin infiltration (%)           | 0                  | 10             | 0              | 0            | 0           | 0             |
| Median survival (mo)            | 103+               | 25             | 120+           | 21           | 16          | 23            |
| Percent with abnormal karyotypes| 13                 | 20             | 29             | 89           | 80          | 0             |
| Percent transforming to ANLL    | 0                  | 20             | 7              | 56           | 40          | 33            |

AISA, acquired idiopathic sideroblastic anemia; CMMoL, chronic myelomonocytic leukemia; RA, refractory anemia; RAEB, refractory anemia with excess blasts; RAEB-T, refractory anemia with excess blasts in transformation; ANLL, acute nonlymphocytic leukemia; Hgb, hemoglobin; WBC, white blood cells.
Skin infiltration by leukemia cells was also seen in one patient with CMMoL.

Although none of these patients had previously received chemotherapy or radiotherapy, one patient within each FAB subtype had a history of exposure to potentially mutagenic agents in the environment. One patient with AISA reported 18 years of exposure to industrial chemicals. Patient No. 21 with CMMoL was a sheet metal worker who eventually developed acute myelomonocytic leukemia. Both were cytogenetically normal at diagnosis, but the latter patient demonstrated a clonal abnormality at the time of transformation to ANLL. Patient No. 3 with RA was employed for several years in a battery factory and, at diagnosis, had a del(5q); this patient’s condition has remained stable for more than 31 months. Patient No. 11 with RAEB was employed in a paint factory and in asphalt road construction. His initial marrow specimen study revealed monosomy 7; 40 months after diagnosis, he developed acute myeloblastic leukemia with maturation (M2). Patient No. 18, with RAEB-T, had been an industrial hygiene inspector and had a del(7)(q22q36). His disease transformed to ANLL four months after diagnosis and he remains alive with disease.

No consistent treatment approach was taken with these patients because they were seen over a 12-year period. Methods of treatment varied within the FAB subtypes of MDS. In general, patients received platelet and red blood cell transfusions whenever necessary. Other therapeutic agents used for some patients included folic acid, vitamin B,2, pyridoxine, steroids, and subcutaneous cytarabine. Among the 11 patients who had transformation to ANLL, only one (patient no. 19) received cytotoxic therapy (subcutaneous cytarabine) prior to transformation. Three patients (nos. 8, 9, and 17) received high-dose cytarabine (2 to 3 g/m²) as primary treatment for their MDS, after other measures to correct severe thrombocytopenia had failed. Patient no. 8 subsequently died of gastrointestinal bleeding and sepsis while granulocytopenic. Patient no. 9 has had an unmaintained complete response for more than 11 months. Patient no. 17 had a complete hematologic and cytogenetic remission for one year but later relapsed and died of refractory leukemia.

The actuarial survival calculated for each FAB subtype of MDS is shown in Fig. 1. For patients with AISA, the cumulative proportion surviving at 24 months was 80%, and the longest survivor was alive at 103 months. For patients with RA, the cumulative proportion surviving at 24 months was 89%, and the longest survivor was alive at 120 months. The median survival times for patients with CMMoL, RAEB, and RAEB-T were 25 months, 21 months, and 16 months, respectively. Patients with AISA and RA had median survivals that were significantly better than those for CMMoL, RAEB, and RAEB-T combined.

Of the 49 patients in this series, 19 had a clonal chromosomal abnormality at diagnosis. Of these, there were seven deaths due to ANLL, two deaths due to the primary MDS, and three deaths due to unrelated or unknown causes. In comparison, of the 30 patients with normal karyotypes, 14 have died; three deaths were due to ANLL, five to the primary MDS, and six to unrelated causes. The median survival for patients with a normal karyotype at diagnosis was 48 months, and for patients with an abnormal karyotype, 32 months. This difference was not statistically significant (P = 0.2). The actuarial survival curves for patients grouped according to normal and abnormal initial karyotypes are shown in Fig. 2.

Transformation to ANLL was observed in 11 patients (22%), after a median interval of 8 months following the diagnosis of MDS (see Table 2). The median survival following transformation to ANLL was one month. Of the patients who developed ANLL, one initially had RA, two had CMMoL, five had RAEB, two had RAEB-T, and one was unclassifiable. The most frequent FAB subtypes of ANLL were myeloblastic leukemia with maturation (M2) in four patients and acute myelomonocytic leukemia (M4) in three patients; one patient had acute myeloblastic leukemia

![Fig 1. Actuarial survival in months according to FAB subtype.](image1)

![Fig 2. Actuarial survival according to the presence of a normal versus an abnormal karyotype at diagnosis.](image2)
Trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients. The cytogenetic abnormalities are shown in Table 2. The most frequent abnormalities were trisomy 8 in five patients, ANLL that could not be readily subclassified according to FAB criteria.

**Cytogenetic analyses.** For the 19 patients who had an abnormal karyotype at the time of diagnosis of MDS, details of the cytogenetic abnormalities are shown in Table 2. The most frequent abnormalities were trisomy 8 in five patients, del(5q) in three patients, and del(20q) in three patients. Each of these was also noted as an evolutionary change, with trisomy 8 occurring most often. These abnormalities were occasionally found together in the same patient, usually as a result of evolution of the initial abnormal karyotype.

<table>
<thead>
<tr>
<th>Patients With Cytogenetic Abnormalities at Diagnosis</th>
<th>MDS Subtype</th>
<th>Patient No.</th>
<th>Age/ Sex</th>
<th>Survival After Diagnosis (Mo)</th>
<th>Survival After Transformation to ANLL (Mo)</th>
<th>FAB Subtype</th>
<th>Number of Metaphase Cells Examined</th>
<th>% BM Cells With Normal Karyotype</th>
<th>Karyotype of Abnormal Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>2</td>
<td>28/F</td>
<td>25+</td>
<td>BM</td>
<td>24, 48M</td>
<td>25</td>
<td>17</td>
<td>46,XX,del(11)(q23)(88%)/47.sane, +6(12%)/45.sane, -20(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>3</td>
<td>59/M</td>
<td>42+</td>
<td>BM</td>
<td>24, 48M</td>
<td>20</td>
<td>35</td>
<td>46,XX,del(11)(q23)(88%)/45.sane, -20(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>4</td>
<td>36/F</td>
<td>57+</td>
<td>BM</td>
<td>24, 24M</td>
<td>23</td>
<td>70</td>
<td>46,XX,del(13)(q11)(14)(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>5</td>
<td>49/F</td>
<td>8+</td>
<td>BM</td>
<td>24, 24M</td>
<td>8</td>
<td>63</td>
<td>46,XX,del(20)(q13)(q11)(37%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>6</td>
<td>71/M</td>
<td>31+</td>
<td>BM</td>
<td>D, 24</td>
<td>16</td>
<td>31</td>
<td>46,XX,del(13)(q11)(14)(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>7</td>
<td>85/M</td>
<td>3+</td>
<td>BM</td>
<td>D</td>
<td>19</td>
<td>0</td>
<td>47.XY, +8(100%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>8</td>
<td>62/M</td>
<td>16+</td>
<td>BM</td>
<td>24, 48M</td>
<td>21</td>
<td>30</td>
<td>46,XX,del(11)(q23)(88%)/45.sane, -20(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>9</td>
<td>76/M</td>
<td>16+</td>
<td>BM</td>
<td>24, 48M</td>
<td>49</td>
<td>19</td>
<td>47.XY, +8(81%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>10</td>
<td>76/F</td>
<td>79</td>
<td>BM</td>
<td>13</td>
<td>54</td>
<td>54</td>
<td>46,XX,del(20)(q13)(34)(68%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>11</td>
<td>56/M</td>
<td>42</td>
<td>BM</td>
<td>15</td>
<td>20</td>
<td>20</td>
<td>45.XY, -7(10)%</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>12</td>
<td>61/F</td>
<td>2.5</td>
<td>M2</td>
<td>48M</td>
<td>15</td>
<td>0</td>
<td>45.XY, -7del(2)(p11)(13)(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>13</td>
<td>68/F</td>
<td>24</td>
<td>BM</td>
<td>24</td>
<td>20</td>
<td>30</td>
<td>45.XY, +8(13)(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>14</td>
<td>75/M</td>
<td>15</td>
<td>BM</td>
<td>48M</td>
<td>15</td>
<td>73</td>
<td>46,XY, +8(100%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>15</td>
<td>68/M</td>
<td>15</td>
<td>BM</td>
<td>D, 24</td>
<td>15</td>
<td>93</td>
<td>47.XY, +8(73%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>16</td>
<td>62/F</td>
<td>3.1</td>
<td>M4</td>
<td>BM</td>
<td>37</td>
<td>100</td>
<td>46.XY</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>17</td>
<td>68/F</td>
<td>3</td>
<td>BM</td>
<td>D, 24</td>
<td>27</td>
<td>67</td>
<td>46.XY, +8(73%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>18</td>
<td>29/M</td>
<td>24</td>
<td>BM</td>
<td>24, 48M</td>
<td>20</td>
<td>5</td>
<td>46,XY,del(11)(q23)(88%)/45.sane, -20(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>19</td>
<td>48/F</td>
<td>27</td>
<td>Unclassifiable</td>
<td>PB</td>
<td>12</td>
<td>0</td>
<td>46,XY,del(20)(q13)(q11)(20%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>20</td>
<td>65/M</td>
<td>2</td>
<td>M4</td>
<td>BM</td>
<td>12</td>
<td>0</td>
<td>46,XY, +11+11(100%)</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>21</td>
<td>57/F</td>
<td>24</td>
<td>Noted at Unclassifiable Autopsy</td>
<td>24</td>
<td>30</td>
<td>86</td>
<td>46,XX,del(20)(q13)(q11)(17)%</td>
</tr>
<tr>
<td>trisomy 8 occurring most often. These abnormalities were del(5q) in three patients, and del(20q) in three patients.</td>
<td>RA</td>
<td>22</td>
<td>25/F</td>
<td>22</td>
<td>M5a</td>
<td>BM</td>
<td>12</td>
<td>83</td>
<td>46,XX,del(20)(q13)(q11)(17)%</td>
</tr>
</tbody>
</table>

*BM, bone marrow; PB, peripheral blood
†D, direct preparations; 24, cells cultured for 24 hours; 24M and 48M, cells cultured in phytohemagglutinin-leukocyte conditioned medium and synchronized with methotrexate for 24 and 48 hours, respectively
‡Karyotype at transformation to ANLL
§Two or more independent clones

without maturation (M1), and one had poorly differentiated monoblastic leukemia (M5a). Two patients developed ANLL that could not be readily subclassified according to FAB criteria.
typical t(9;22) and has been reported on in detail.20 Patient No. 12 with a del(5q) had a complex pattern of related chromosomally abnormal clones. When the first sample was obtained from this patient, the largest clone (45%) had a translocation of unidentified material to 6p(p23 or 25) as well as an interstitial deletion of 9q resulting in loss of bands q13q22 or q22q34. Although the patient did not have the typical t(6;9)(p23;q34) which may be associated with increased marrow basophilia,21 a complex rearrangement resulting in the juxtaposition of the critical genes on 6p23 and 9q34 could have occurred. This interpretation was suggested by the fact that the marrow from this patient contained 25% basophils.

The association of a specific karyotypic abnormality with the MDS subtypes appeared variable. Thus, a +8 was seen in all groups except RA, and it was present in one-half of the patients with RAEB, either initially or after evolution. A del(5q) was observed in both RA and RAEB, whereas all three patients with the del(20q) had RAEB. Loss of No. 7 and del(7q) were noted in RAEB and RAEB-T, respectively. The other abnormalities were randomly distributed throughout the subgroups. Overall, a clonal abnormality was detected in one of the eight patients with AISA, in two of the ten with CMMoL, in four of the 14 with RA, in eight of the 19 patients with an initially normal karyotype who later developed ANLL, two had CMMoL. In one of these, acute leukemia was unexpectedly found at autopsy, and analysis of the karyotype was not repeated. When the second patient developed ANLL, 100% of his bone marrow cells had the karyotype 48,XY,+11,+11. The third patient had an unclassified type of MDS; the karyotype at transformation was 46,XX in 83% of cells and 46,XX,t(9;?)q21;?) in 17%.

**Morphologic features.** Every patient in the study showed evidence of some dyspoiesis in at least one marrow cell line. Severe dysplasia, as described by Juneja et al.,23 was found in at least one cell line in 36 of the patients. Nine patients initially had severe dysplasia in two cell lines, and 10 additional patients had severe (trilineage) dysplasia in the granulocytic, erythroid, and megakaryocytic cell lines. These latter 10 patients were in the RAEB (2 patients), RAEB-T (3 patients), CMMoL (3 patients), and unclassified (2 patients) categories. Five of the 10 patients (50%) with severe trilineage dysplasia had transformation to ANLL, compared to 15% of those without severe trilineage dysplasia (P < .05). In addition, 10 of the 11 patients (91%) whose disease transformed to ANLL had severe dysplasia initially in at least two cell lines (seven in the granulocytic and megakaryocytic lines, and three in the erythroid and megakaryocytic lines). The median survival time of patients with trilineage dysplasia was 23 months, compared to 46 months for patients without such extensive dysplasia. The difference in survival times of patients, regardless of whether ANLL supervened, approached statistical significance based on the degree and extent of dyspoiesis (P = .05). There was no significant correlation between karyotypic abnormalities and the severity of dysplasia.

**Clinical correlations with cytogenetic abnormalities.** Eight of the 19 (42%) patients with an initially abnormal karyotype developed ANLL, compared to three of the 30 (10%) patients with a normal karyotype. Thus, there was a significant association between the presence of an initial chromosome abnormality and the subsequent development of ANLL (P < .01). Among patients with RA, RAEB, or RAEB-T, the risk of ANLL was confined to those with an abnormal karyotype (8/16 v 0/12 with a normal karyotype; P < .01).

In this small series, it is difficult to establish whether patient survival from the time of diagnosis or the length of time to transformation to ANLL was related more closely to the chromosome pattern or to the FAB subtype of the MDS. There appears to be no correlation between the karyotype and specific subtypes of MDS, except possibly for del(20q) and RAEB. Of the five patients with trisomy 8, four have died, and the fifth developed ANLL; survival from the time of diagnosis was relatively short (3 to 16 months). In contrast, although all three patients with del(20q) have died (one after ANLL), their survival times ranged from 16 to 79 months. The two patients (Nos. 11 and 18) with abnormalities in chromosome No. 7 had marked differences (39.5 months and 4 months, respectively) in the length of the preleukemic phase of their disease before transformation to ANLL. Two patients (No. 2 and No. 3) with RA and del(5q) showed this aberration alone or as a mosaic of two abnormal clones; both patients are alive at 25 and 42 months, respectively. In contrast, two patients (No. 12 and No. 14) with RAEB had del(5q) as part of a complex karyotype, and their MDS transformed to ANLL. Patient No. 12 developed ANLL after 4 months, Patient No. 14 had two independent clones and developed a third independent clone with del(5q) at the time of transformation to ANLL, 8 months after the diagnosis of MDS.

Of the three patients (Nos. 20 to 22) with an initially normal karyotype who later developed ANLL, two had CMMoL. In one of these, acute leukemia was unexpectedly found at autopsy, and analysis of the karyotype was not repeated. When the second patient developed ANLL, 100% of his bone marrow cells had the karyotype 48,XY,+11,+11. The third patient had an unclassified type of MDS; the karyotype at transformation was 46,XX in 83% of cells and 46,XX,t(9;?)q21;?) in 17%.
patient no. 2, the single patient in this study who had a del(5q) as the sole chromosomal aberration. This patient, classified as RA, showed minimal dyserythropoiesis and dysgranulopoiesis. There has been no change in her disease over 4 years. Similar megakaryocytic abnormalities were present in two additional patients (nos. 3 and 12), both of whom had a del(5q) in combination with other chromosome changes. Both of these patients also had severe dyserythropoiesis at the time of diagnosis and one had an increased number of blasts.

**DISCUSSION**

We have described the clinical features, cytogenetic abnormalities, and morphologic findings in 49 patients with primary MDS. Correlations were sought among subsets of patients classified according to the morphologic criteria of the FAB group. Taken together, the cytogenetic and morphologic findings identified subsets of prognostic importance.

Our data indicate that particular chromosomal abnormalities are not associated with specific FAB subtypes, with the possible exception of del(20q) in RAEB. However, we found the presence of a cytogenetic abnormality at diagnosis to have prognostic significance. In our series, 39% of patients had a cytogenetic abnormality at diagnosis (median survival, 32 months); 42% of these developed ANLL compared to only 10% of those with a normal karyotype (median survival, 48 months). Comparable results have been reported by other investigators.\(^{10,22,24}\) At the Second Workshop, patients with cytogenetic abnormalities had progressed to ANLL more often than had those with a normal karyotype (27% vs 15%, \(P < 0.05\)).\(^\text{10}\) Todd and Pierre also noted a significant difference in median survivals between patients with normal and abnormal karyotypes (3.4 vs 1.85 years, respectively; \(P < 0.004\)).\(^\text{24}\)

Two patients (nos. 12 and 14) had several independent abnormal clones; this is rarely observed in ANLL de novo. The unexpectedly high incidence of multiple independent clones in the present series may be an important feature of MDS, although its significance is unclear at present.

The most frequent cytogenetic abnormality seen in our series was trisomy 8 which is common both in ANLL de novo and in primary MDS at the time of transformation to ANLL.\(^{9,10,25}\) The prognostic significance of other karyotypic abnormalities, such as del(5q), is unclear.\(^{8,26}\) In the present study, the two patients who had a clone with only a 5q- had RA and apparently stable disease. On the other hand, both patients with a complex karyotype including a 5q- abnormality had RAEB that later transformed to ANLL. Whether the complex karyotype was “responsible” for a more dysplastic marrow with a greater likelihood of ANLL, or whether the degree of dysplasia was independent of the karyotype is uncertain.

An interstitial deletion of the long arm of chromosome 20 (breakpoints q11.2 and q13.3) was seen in three of our patients, all of whom had RAEB. Del(20q) is uncommon among patients with ANLL de novo or therapy-related ANLL but has been observed in some patients with polycythemia vera, AISA, and other myeloproliferative disorders.\(^{27-29}\)

Two patients in our series had deletions involving chromosome 7, and both had histories of exposure to potentially mutagenic materials. By comparison, among 47 patients with therapy-related MDS evaluated at the University of Chicago, 45 (96%) had clonal abnormalities involving either chromosome 5 or chromosome 7.\(^\text{30}\)

In our study, the prognostic value of the FAB classification system for MDS was confirmed, as it has been by others. None of our patients with AISA had transformation to ANLL. Other investigators have also reported that patients with AISA had a relatively benign course, with a median survival time of about ten years.\(^\text{31}\) Seven to 25% of patients reported in other series, however, eventually developed ANLL.\(^{13,31,32}\)

As defined by the FAB criteria, RA, RAEB, and RAEB-T differ in the number of blasts present in the peripheral blood and bone marrow, the presence or absence of Auer rods, and the lack of severe dysplasia in RA.\(^\text{6}\) In our series, patients with RA were less likely to develop ANLL and had longer survival times than did patients with RAEB and RAEB-T. In two other studies, ANLL developed in 18% and 55% of patients with RAEB.\(^{15,33}\) Thus, RAEB and RAEB-T are more often “preleukemic” disorders or the “forme fruste” of a rapidly progressive hematopoietic neoplasm.

CMMoL is a poorly defined disorder characterized by monocytosis, usually occurring in elderly patients. These patients appear to have a poor prognosis independent of cytogenetic abnormalities at diagnosis. In our series, neither of the patients who had chromosomal abnormalities at diagnosis developed ANLL, but two with normal karyotypes did have transformation to ANLL. Death was most frequently due to progressive bone marrow failure. Solal-Celignay et al have reported a median survival time of 475 days in 35 patients with CMMoL, 20% of whom developed ANLL.\(^\text{34}\) In another series, 30% of all patients eventually developed ANLL.\(^\text{35}\)

Several attempts have been made to define other morphologic parameters that provide prognostic information in MDS in addition to the FAB subtype.\(^{4,36-38}\) In this series, additional prognostic information was obtained using a scoring system for the severity of dysplasia, similar to that used by Juneja et al.\(^\text{15}\) Patients with severe dyspoiesis in two or three cell lines were much more likely to develop ANLL than those with less severe abnormalities; severe abnormalities in the megakaryocytes were especially ominous. This finding is in agreement with Varella et al, who also emphasized the prognostic import of dysmegakaryocytopenia and dysgranulopoiesis for leukemic progression.\(^\text{39}\)

Like Tricot et al,\(^\text{16}\) we found that ALIP was associated with shorter survival times and an increased incidence of ANLL, but we did not find an association between ALIP and cytogenetic abnormalities at diagnosis. In both studies, the majority of patients with ALIP had CMMoL, RAEB, or RAEB-T. However, unlike Tricot, we found a significant
survival advantage for patients with RA and AISA (median survival not reached at 120 months) compared to those with CMMoL, RAEB, and RAEB-T (median survival, 22 months) ($P = .0004$). Thus, we conclude that ALIP is strongly associated with the FAB subtype, and in our series, offered no additional prognostic information.

Taken together, the morphologic findings and cytogenetic abnormalities at diagnosis can identify patients with primary MDS who have a high likelihood of developing ANLL and whose survival times are limited. In this group of patients with a poor prognosis, the early use of intensive chemotherapy to eradicate the malignant clone prior to the emergence of overt leukemia may be justifiable. In contrast, the use of cytotoxic therapy in patients with features suggesting a good prognosis is unwarranted.

ACKNOWLEDGMENT

The authors wish to acknowledge the many physicians in the Chicago area who referred patients to the University of Chicago for these studies. Many technicincs in the Cytogenetics Laboratory of the Joint Section of Hematology/Oncology provided expert technical assistance. We thank A. Joyce Trice for preparing the manuscript and Elisabeth Lanzl for editorial assistance.

REFERENCES

32. Bitran J, Golomb HM, Rowley JD: Idiopathic acquired
Prognostic implications of morphology and karyotype in primary myelodysplastic syndromes

RH Jacobs, MA Cornbleet, JW Vardiman, RA Larson, MM Le Beau and JD Rowley