# Bone Marrow Dysplasia in Patients with Newly Diagnosed Acute Myelogenous Leukemia Does Not Correlate with History of Myelodysplasia or with Remission Rate and Survival

*Karen K. Ballen, M.D.,* D. Gary Gilliland, M.D., Ph.D.,* Leslie A. Kalish, D.Sc.,† and Lawrence N. Shulman, M.D.**

Background. The records and initial bone marrow studies of 106 patients with newly diagnosed acute myelogenous leukemia (AML) were analyzed retrospectively to determine whether bone marrow dysplasia was predictive of a previous myelodysplastic disorder or correlated with remission rate and survival.

Methods. Bone marrow aspirates and biopsy specimens were reviewed in a blinded fashion; dysplasia was assessed in as objective a manner as possible by numerically scoring nine specific findings: erythrocyte multinuclearity, nuclear fragmentation, megaloblastic characteristics, leukocyte granulation abnormalities and nuclear malformations, Pelger–Huet cells, and megakaryocytic dysplasia (mononuclear megakaryocytes, micromegakaryocytes, and megakaryocytes with multiple distinct nuclei).

Results. Dysplasia of the megakaryocytic line was seen in 34% of patients; 70% of the patients had erythrocyte dysplasia; and 68% had leukocyte dysplasia. Pelger–Huet cells were seen in bone marrow of 35% of the patients. Overall dysplasia score and specific dysplastic findings such as Pelger–Huet cells did not correlate with a known history of myelodysplasia ($P = 0.47$), cytogenetic abnormalities ($P = 0.35$), prior chemotherapy treatment with or without alkylating agents ($P = 1.00$), previous malignant disorders such as polycythemia vera ($P = 1.00$), remission rate ($P = 0.93$), or survival ($P = 0.42$). Multivariate analysis confirmed known independent risk factors for remission in this patient population, including age ($P = 0.04$), history of prior chemotherapy ($P = 0.04$), abnormalities in chromosomes 5, 7, or 8 ($P = 0.02$), and type of antileukemia therapy ($P < 0.001$).

Conclusions. Bone marrow dysplasia is common in patients with AML and does not correlate with a history of myelodysplasia or predict outcome when patients are treated with standard intensive AML therapy. Cancer 1994;73:314–21.

Key words: acute myelogenous leukemia, myelodysplasia, bone marrow.

Acute myelogenous leukemia (AML) is a heterogeneous clonal disorder characterized by early myeloid precursors that have largely, but not entirely, lost their ability to differentiate into mature progeny.[1–3] If some degree of maturation occurs, dysplastic erythrocytes, leukocytes, and megakaryocytes may be present.[4]

Patients with AML who have a previous history of myelodysplastic syndrome, a previous hematologic disorder such as polycythemia vera, a history of therapy with alkylating agents, or certain specific chromosomal abnormalities have lower remission and survival rate than do patients with de novo AML.[5–9] Morphologic examination of the bone marrow for dysplasia has been used to determine whether patients with AML have pre-existing myelodysplastic syndrome, and some studies have suggested that dysplasia can predict remission. For example, in one study 45% of patients with severe dysplasia and 73% of patients with minimal dysplasia had disease enter remission.[1]

We reviewed 106 consecutive patients with newly diagnosed AML to determine whether bone marrow dysplasia correlated with clinical patient characteristics at diagnosis (history of myelodysplasia, previous hema

Presented in part at the American Society of Hematology meetings, Denver, Colorado, December 1991.

From the *Hematology-Oncology Division, Brigham and Women's Hospital, Harvard Medical School, and the †Division of Biostatistics, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts.

Address for reprints: Karen K. Ballen, M.D., Hematology-Oncology Division, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115.

Accepted for publication August 16, 1993.

nologic disorder, previous treatment with alkylating agents, specific chromosomal abnormalities known to be associated with myelodysplasia) and with attainment of complete remission and survival. An objective numerical dysplasia score was assigned based on a blinded review of bone marrow aspirates and biopsy specimens. Statistical analyses were performed to explore the independent contributions of patient and bone marrow characteristics in predicting remission and survival.

## Materials and Methods

Medical records of 106 consecutive patients with bone marrow examinations available who were seen at the Brigham and Women's Hospital between 1982 and 1989 with newly diagnosed AML were reviewed. Age, sex, French–American–British (FAB) classification, karyotype, blood counts before and at diagnosis, documented history of myelodysplasia, prior malignant disorder, and prior therapy with chemotherapy agents were recorded. A history of myelodysplasia was noted if the patient had a documented bone marrow diagnosis of myelodysplasia more than 3 months before the diagnosis of AML. Malignant disorders included solid tu- —, the terminal phase of polycythemia vera and myeloid metaplasia, and diseases associated with therapy-related AML such as Hodgkin's disease. Treatments, including chemotherapy regimen, and disease remission and patient survival rates were analyzed. Patients who eventually had a bone marrow transplant were included.

### *Bone Marrow Morphology Review*

Bone marrow aspirates and biopsy specimens were reviewed on all 106 patients by three authors (K.K.B., D.G.G., L.N.S.) in a blinded fashion, without knowledge of patient name or history. In most patients (79), both aspirates and biopsy specimens were reviewed. For five patients, only a bone marrow biopsy specimen was available. In 22 patients, only the bone marrow aspirate was reviewed. Evaluation was based on bone marrow aspirates and biopsy specimen, when available. Some characteristics, such as hypogranulation, were more easily ascertained from the aspirate, whereas other characteristics, such as percent cellularity, could be obtained only from biopsy specimen.

The percentage cellularity, presence or absence of Auer rods, percentage myeloblasts, myeloid:erythroid ratio, and presence or absence of bone marrow fibrosis were evaluated. Specific dysplastic characteristics were graded. Megakaryocytes were scored individually for the presence of micromegakaryocytes, mononuclear megakaryocytes, and megakaryocytes with multiple small, distinct nuclei. A micromegakaryocyte was defined as less than one-third normal size, approximately less than 25 $\mu$m in diameter. Erythrocytes were examined for multinuclearity, nuclear fragmentation, and megaloblastic changes. Leukocytes were graded for granulation abnormalities, nuclear segmentation abnormalities, and Pelger–Huet cells.[10] Granulation abnormalities were defined as a lack of granules in the cytoplasm. Nuclear segmentation abnormalities included hypolobular and pseudo-Pelger–Huet abnormalities.

Individual characteristics of leukocyte and erythrocyte dysplasia (Table 1) were graded from 1 to 4, with 1 representing no dysplasia; 2, mild dysplasia; 3, moderate dysplasia; and 4, marked dysplasia. Because many of the bone marrow specimens did not have evaluable megakaryocytes or had few megakaryocytes to review, megakaryocytic dysplastic features were scored as mild or marked. Three to four low-power (×10) and 10 high-power (×100) fields were examined for each specimen. A characteristic was scored as mild if less than 10% of a cell line was abnormal; moderate, if 10–30% of the cells of that lineage exhibited this specific characteristic; and marked, if more than 30% of the cell line showed the particular dysplastic characteristic. For example, the presence of a rare Pelger–Huet cell earned a score of mild Pelger–Huet dysplasia; if 20% of the erythrocytes were megaloblastic, this was scored as moderate megaloblastic changes; and if 50% of the megakaryocytes were mononuclear, the bone marrow was considered to have marked mononuclear megakaryocytic dysplasia. Each cell type was given a dysplasia score, and all scores were added for an overall dysplasia score. Cell types that could not be evaluated, because insufficient numbers (fewer than 25) of these cells were present, were marked as not evaluable and assigned the average score. Nonevaluable patients were excluded from some of the statistical analyses, as discussed in Results.

Complete remission was defined as less than 5% blasts in a normocellular or hypercellular bone marrow with normal peripheral blood counts. Survival times were measured from the date of diagnosis.

### *Statistical Analysis*

The Wilcoxon midrank test was used to test for association between a dichotomous outcome (e.g., remission) and ordered categorical variates (e.g., none, mild, moderate, marked dysplasia), and Fisher's exact test was used to test for association with unordered categorical covariates.[11,12] The logistic regression model was used to assess simultaneously the association of more than one covariate with remission.[13] Survival probabilities

**Table 1. Bone Marrow Dysplasia Scoring and Remission Rate (N = 106)**

| | No. | Remission rate (%) | *P* value |
|---|---|---|---|
| Micromegakaryocytes | | | 0.74 |
| Not evaluable | 61 | 50 | |
| Absent | 18 | 55 | |
| Mild increase | 18 | 56 | |
| Marked increase | 9 | 56 | |
| Mononuclear megakaryocytes | | | 0.92 |
| Not evaluable | 61 | 56 | |
| Absent | 15 | 53 | |
| Mild increase | 22 | 55 | |
| Marked increase | 8 | 50 | |
| Multiple nuclei megakaryocytes | | | 0.58 |
| Not evaluable | 62 | 55 | |
| Absent | 20 | 55 | |
| Mild increase | 14 | 57 | |
| Marked increase | 10 | 60 | |
| Overall megakaryocyte dysplasia | | | 0.71 |
| Not evaluable | 65 | 54 | |
| None | 7 | 57 | |
| Mild | 18 | 61 | |
| Moderate | 9 | 44 | |
| Marked | 7 | 57 | |
| Erythrocyte multinuclearity | | | 0.95 |
| Not evaluable | 26 | 54 | |
| Absent | 33 | 55 | |
| Mild increase | 19 | 53 | |
| Moderate increase | 16 | 63 | |
| Marked increase | 12 | 50 | |
| Erythrocyte nuclear fragmentation | | | 0.98 |
| Not evaluable | 26 | 54 | |
| Absent | 25 | 60 | |
| Mild increase | 21 | 48 | |
| Moderate increase | 18 | 50 | |
| Marked increase | 16 | 63 | |
| Erythrocyte megaloblasts | | | 0.46 |
| Not evaluable | 26 | 54 | |
| Absent | 12 | 50 | |
| Mild increase | 27 | 56 | |
| Moderate increase | 29 | 48 | |
| Marked increase | 12 | 75 | |
| Overall erythrocyte dysplasia | | | 0.85 |
| Not evaluable | 27 | 56 | |
| None | 9 | 56 | |
| Mild | 36 | 53 | |
| Moderate | 20 | 55 | |
| Marked | 14 | 57 | |
| Leukocyte granulation abnormalities | | | 0.84 |
| Not evaluable | 30 | 53 | |
| Absent | 12 | 42 | |
| Mild increase | 37 | 59 | |
| Moderate increase | 22 | 64 | |
| Marked increase | 5 | 20 | |
| Leukocyte nuclear segmentation abnormalities | | | 094 |
| Not evaluable | 30 | 53 | |
| Absent | 13 | 46 | |
| Mild increase | 34 | 59 | |
| Moderate increase | 24 | 63 | |
| Marked increase | 5 | 20 | |
| Pelger cells | | | 0.52 |
| Not evaluable | 28 | 54 | |
| Absent | 43 | 58 | |
| Mild increase | 21 | 52 | |
| Moderate increase | 11 | 55 | |
| Marked increase | 3 | 33 | |
| Overall leukocyte dysplasia | | | 0.71 |
| Not evaluable | 29 | 55 | |
| None | 9 | 33 | |
| Mild | 41 | 59 | |
| Moderate | 22 | 64 | |
| Marked | 5 | 20 | |
| Overall impression of dysplasia | | | 0.93 |
| Not evaluable | 16 | 56 | |
| None | 6 | 33 | |
| Mild | 42 | 60 | |
| Moderate | 34 | 53 | |
| Marked | 8 | 50 | |

were estimated by the method of Kaplan and Meier.[14] The log-rank test, log-rank test for trend, and proportional hazards model were used to test for associations with survival.[15–17] *P* values less than 0.05 were considered significant.

## Results

Clinical characteristics of the 106 patients in the study are shown in Table 2. The average age was 57 years, and 51% of the patients were men. FAB types M2 and M4 were the most common. Corresponding remission rates and tests for association with remission and survival are shown in Table 3. Thirty-eight percent of patients had a known cytogenetic abnormality; abnormalities of chromosomes 5, 7, and 8 were associated with a worse prognosis. Twenty-five percent of patients had a history of myelodysplasia; as anticipated, these patients had lower disease remission rates. Patients who had a history of a prior malignant disorder (22%) and those who had received prior chemotherapy (11%) also had

**Table 2. Patient Characteristics**

| patient characteristics | No. |
|---|---|
| Overall group | 106 |
| **Age (yr)** | |
| < 21 | 3 |
| 21–40 | 20 |
| 41–60 | 25 |
| 61-80 | 55 |
| > 80 | 3 |
| *sex* | |
| Female | 52 |
| Male | 54 |
| FAB classification | |
| M1 | 17 |
| M2 | 38 |
| M3 | 5 |
| M4 | 28 |
| M5 | 8 |
| M6 | 6 |
| M7 | 4 |
| **Chromosomes** | |
| Normal | 32 |
| t(8;21) | 2 |
| t(15;17) | 5 |
| inv 16 | 1 |
| Abnormal chromosome 5 | 6 |
| Abnormal chromosome 7 | 9 |
| Abnormal chromosome 8 | 8 |
| *Other* abnormal chromosomes | 9 |
| unknown | 34 |
| History of myelodysplasia | |
| None | 79 |
| Refractory anemia | 8 |
| Refractory anemia—excess blasts | 7 |
| Refractory anemia—transformation | 6 |
| Sideroblastic anemia | 5 |
| CMML | 1 |
| Prior hematologic diagnosis | |
| None | 83 |
| Lymphoma | 3 |
| Breast cancer | 1 |
| Polycythemia | 2 |
| Myelofibrosis | 6 |
| Hodgkin's | 1 |
| *other* | 10 |
| Prior Chemotherapy | |
| None | 94 |
| Alkylating agent | 7 |
| Nonalkylating | 5 |
| Induction chemotherapy | |
| None | 10 |
| Hydroxyurea | 11 |
| DNR and ARA-C 2 and 5' | 4 |
| DNR and ARA-C 3 and 7* | 43 |
| DNR and ARA-C 3 and 7*/HIDAC | 11 |
| DNR and ARA-C 3 and 7*/6TG | 2 |
| Other | 23 |
| Unknown | 2 |

DNR: daunorubicin-, 45–60 mg/m²/d; Ara-C: cytosine arabinoside, 100–200 mg/m²/day; HIDAC: ara-C, 4 g/m²/d for 3 d; 6TG: 6-thioguanine, 200 mg/m²/day; FAB: French-American-British; MML chronic myelomecrocytic leukemia.

* Numbers refer to days of administration of daunorubidn and Ara-C, respectively.

**Table 3. Association of Patient Characteristics With Remission and Survival**

| | N | Remission (%) | Remission *P* value | Survival *P* value |
|---|---|---|---|---|
| All cases | 106 | 55 | — | — |
| **Age (yr)** | | | < 0.001 | 0.001 |
| ≤ 40 | 23 | 91 | | |
| 41–60 | 25 | 64 | | |
| > 60 | 58 | 36 | | |
| Sex | | | 0.55 | 0.53 |
| Female | 52 | 58 | | |
| Male | 54 | 52 | | |
| FAB classification | | | 0.54 | 0.93 |
| M1 | 17 | 41 | | |
| M2 | 38 | 47 | | |
| M3 | 5 | 80 | | |
| M4 | 28 | 64 | | |
| M5 | 8 | 63 | | |
| M6 | 6 | 50 | | |
| M7 | 4 | 75 | | |
| Chromosomes | | | 0.05 | 0.09 |
| Unknown | 34 | 50 | | |
| Normal | 32 | 63 | | |
| Abnormal 5, 7, 8 | 23 | 35 | | |
| Other abnormalities | 17 | 76 | | |
| History of myelodysplasia | | | 0.003 | 0.21 |
| No | 79 | 63 | | |
| Yes | 27 | 30 | | |
| Prior malignant diagnosis | | | 0.04 | 0.02 |
| No | 83 | 60 | | |
| Yes | 23 | 35 | | |
| Prior chemotherapy | | | 0.001 | 0.001 |
| No | 94 | 61 | | |
| Yes | 12 | 8 | | |
| Induction chemotherapy | | | < 0.001 | < 0.001 |
| Aggressive | 56 | 86 | | |
| Nonaggressive or none | 48 | 21 | | |
| Unknown' | 2 | 0 | | |

FAB French–American–British.

• Excluded from analysis.

lower remission rates. Blood counts at the time of diagnosis and before diagnosis did not influence remission rate (data not shown).

The type of induction chemotherapy was the strongest predictor of remission rate. Patients who received intensive chemotherapy (defined as daunorubicin 45 mg/m²/day for 3 days and cytosine arabinoside 100–200 mg/m²/day for 7 days, with or without high-dose cytosine arabinoside or 6-thioguanine) were more likely to have disease enter remission ($P < 0.001$).

Table 1 outlines the dysplastic findings on the bone marrow aspirates and biopsy specimens, with corresponding remission rates and the test for correlations between degree of dysplasia and remission rate. Nonevaluable patients were excluded from these tests, although formal tests comparing evaluable with nonevaluable patients did not change the conclusions.

Thirty-two percent of patients had megakaryocytic dysplasia (15% moderate or marked) manifest by micromegakaryocytes, mononuclear megakaryocytes, or megakaryocytes with multiple distinct nuclei. Remission rate did not correlate with the degree of megakaryocytic dysplasia. Sixty-six percent of patients had erythrocyte dysplasia (32% moderate or marked) demonstrated by multinuclearity, nuclear fragmentation, and megaloblastic changes. There was no correlation between remission rate and degree of erythrocyte dysplasia. Sixty-four percent of patients had leukocyte dysplasia (25% moderate or marked) with granulation abnormalities, nuclear malformations, and Pelger–Huet cells. The remission rate was not correlated with the degree of leukocyte dysplasia. Pelger–Huet cells were found in the bone marrow of 33% of patients; the presence of Pelger–Huet cells did not correlate with remission rate. Dysplasia did not correlate with remission rate when measured by overall impression ($P = 0.93$) or by dysplasia score ($P = 0.91$). The percentage of myeloblasts, presence of reticulin, myeloid:erythroid ratio, and presence of Auer rods also did not affect the remission rate. The results are unchanged whether patients had both bone marrow aspirates and biopsy specimens reviewed or only one study examined.

In multivariate analysis, four factors were independent predictors of remission. Prior chemotherapy ($P = 0.04$), older age ($P = 0.04$), abnormalities of chromosomes 5, 7, or 8 ($P = 0.02$), and nonintensive induction chemotherapy ($P < 0.001$) were predictors of lower remission rates. Although prior malignant disorder and a history of myelodysplasia correlated inversely with remission rate by univariate analysis, they were not significant in multivariate analysis because of their correlations with older age and nonintensive chemotherapy, respectively.

The median survival time was 9 months from the date of diagnosis. Forty-six percent of patients were alive at 1 year, 25% at 2 years, and 18% at 3 years. Bone marrow dysplasia at presentation did not correlate with survival. Each measure of dysplasia in Table 1 was tested for association between degree of dysplasia and survival. Results of all tests were nonsignificant, as were results of comparisons of evaluable and nonevaluable patients. There was no correlation between dysplasia and survival when measured by overall impression ($P = 0.42$) or by total dysplasia score ($P = 0.11$). As an example, Figure 1 shows survival of patients with overall impression of dysplasia scored as versus moderate/marked ($P = 0.54$). Type of antileukemic therapy, prior chemotherapy, and patient age were the most important significant predictive factors for survival (Table 3). At 3 years, 32% of patients intensive induction treatment (including patients who subsequently underwent bone marrow transplantation) were alive, compared with none in the group treated with less than intensive therapy.

Morphologic features of dysplasia did not correlate with abnormal karyotype ($P = 0.25$), prior chemotherapy ($P = 1.00$), prior malignant disorder ($P = 1.00$), age ($P = 0.55$), or with a history of myelodysplasia ($P = 0.47$), as outlined in Table 4.

## Discussion

This study attempted to determine if dysplasia in the bone marrow of patients with AML had prognostic significance or correlated with a history of myelodysplasia, previous alkylating agent therapy, or prior hematologic disorder. This analysis was important because AML arising after one of these disorders has a particularly dire prognosis. In addition, in a patient with AML it may not always be clear whether a previous myelodysplastic syndrome was

Realizing that dysplasia is considered a subjective finding, we attempted to make our study as objective as possible by rigorously quantifying cellular characteristics. Objective criteria for dysplasia were established for each hematopoietic lineage. Nine morphologic characteristics were graded, and a numerical dysplasia score was obtained for each characteristic, each cell line, and the bone marrow as a whole. The morphology review was blinded for name, age, and history of the patient We found that some characteristics, such as erythrocyte multinuclearity and Pelger–Huet cells, were easier to quantify than others, such as leukocyte granulation abnormalities. All three observers had to agree before a cell was marked as dysplastic.

Dysplasia was a common finding, with the bone marrow of 32% of patients demonstrating megakaryocytic dysplasia, 66% showing erythrocyte dysplasia 64% exhibiting leukocyte dysplasia, and 33% ha—— Pelger–Huet cells. This high incidence of dysplasia m. ceeded the percent of patients known to have disease arising from a myelodysplastic syndrome (25%), a prior malignant disorder (22%), or alkylating agent therapy (7%).

A high number (25%) of our patients with AML had a history of myelodysplastic syndrome that be documented by bone marrow examination than 3 months before the diagnosis of AML. This high

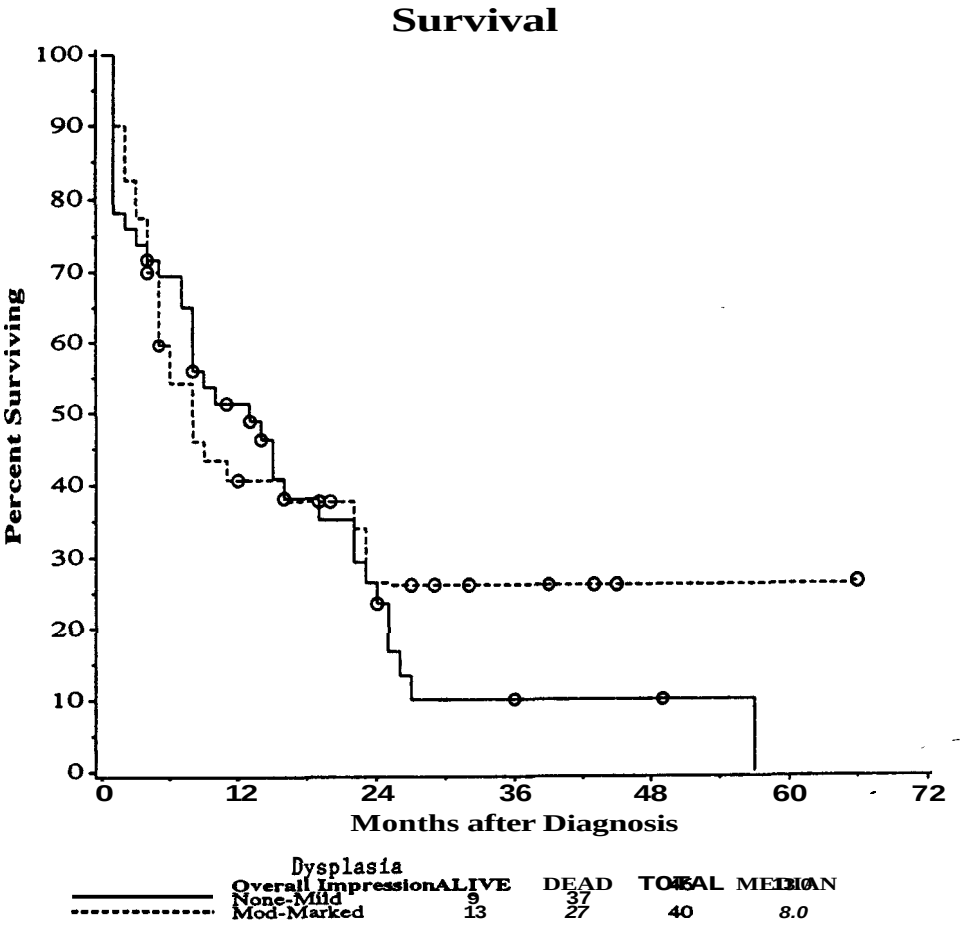


Figure 1. Survival by dysplasia categories ($P = 0.54$). —: none or mild dysplasia; - - -: moderate or marked dysplasia.

incidence of myelodysplasia may be attributed to our referral-based patient population. Our series represents consecutive patients with newly diagnosed AML with all materials available, and thus includes patients with de novo and secondary AML without any selection. The degree of bone marrow dysplasia at time of diagnosis of AML was not different in the de novo group than in the secondary AML group, despite a significant difference in prognosis between these two groups.

Factors that were significant for predicting remission rate in our patients were age, chromosomal abnormalities, prior chemotherapy, and type of induction chemotherapy, all in accordance with previous studies in the literature.[5,6,18–21]

Our results differ from some published studies on morphology in patients with AML.[22,23] Curtis et al.[24] reported that the percentage of bone marrow myeloblasts was inversely related to survival. Brito-Babapulle et al.[25] studied 160 patients with AML. Twenty-four of those patients had evidence of trilineage dysplasia and had a remission rate of 50%, compared with a remission rate of 86% for patients without dysplasia. However, no significant difference in overall survival was found.

Other studies have reported no relationship between remission rate and morphologic features.[26,27] Fenaux et al.[29] reviewed 214 patients, and 30% had trilineage dysplasia. There was no difference in the disease remission rate between patients with and those without dysplasia. A review of morphology by Swirsky et al.[30] found that only Auer rods and eosinophilia were important positive predictors of remission rate, whereas a low platelet count was an adverse factor. Patient age and performance status were the only historic factors found to correlate with survival. Auer rods were found to be positive predictors of survival by Mertelsman et al.[31] Auer rods were found in the leukemic cells of only 17 of our patients, making statistical analysis difficult. A study of 332 patients with de novo AML found that only 11% of patients had trilineage dysplasia. Granulocytic dysplasia was associated with a lower remission rate (57% versus 72%), but erythrocytic and megakaryocytic dysplasia had no effect on remission rate.[32]

**Table 4. Correlation of Bone Marrow Dysplasia With Patient Characteristics**

| | N | Marrow dysplasia* (%) | P value |
|---|---|---|---|
| All evaluable† | 90 | 47 | — |
| Age (yr) | | | 0.57 |
| ≤ 40 | 18 | 56 | |
| 41–60 | 23 | 44 | |
| > 60 | 49 | 45 | |
| Chromosomes | | | 0.35 |
| Unknown | 31 | 42 | |
| Normal | 28 | 43 | |
| Abnormal 5, 7, 8 | 19 | 58 | |
| Other abnormality | 12 | 50 | |
| Myelodysplasia history | | | 0.47 |
| No | 68 | 44 | |
| Yes | 22 | 55 | |
| Prior malignant disorder | | | 1.00 |
| No | 71 | 46 | |
| Yes | 19 | 47 | |
| Prior chemotherapy | | | 1.00 |
| No | 81 | 47 | |
| Yes | 9 | 44 | |

* Percentage of bone marrow specimens scored as moderate or marked dysplasia.

† Sixteen patients were scored as not evaluable and excluded from this analysis.

The etiology of dysplastic cells in patients with AML is unclear. If the leukemic cell is an early progenitor cell common to granulocytes, erythrocytes, and megakaryocytes, all of these lineages will be involved.[1] Fialkow et al.,[3] using patients who are heterozygous for X-chromosome–linked glucose-6-phosphate dehydrogenase, showed that AML develops clonally and is heterogeneous. In some patients, the leukemic stem cell manifests granulocytic, megakaryocytic, and erythrocytic differentiation, whereas in other patients, only the granulocytic line is involved. Using recombinant DNA probes, Fearon et al.[33] demonstrated that in some patients leukemic blast cells can differentiate to form mature cells. We speculate that the dysplastic findings we observed represent incomplete maturation of the leukemic clone.

Our study demonstrates that the presence of specific and trilineage dysplastic findings in the bone marrow of patients with newly diagnosed AML is common, not predictive of a history of myelodysplasia, and is not prognostically significant. Because patients with a previous history of myelodysplasia sometimes are treated differently and less intensively than are patients with presumed de novo AML, dysplastic findings in the bone marrow of patients should not be used to determine whether there may have been a previous myelodysplastic syndrome, which might deny the appropriate intensive chemotherapy.

## References


1. Vellenga E, Griffin JD. The biology of acute myeloblastic leukemia. *Semin Oncol* 1987; 14:365–71.
2. Griffin JD, Lowenberg B. Clonogenic cells in acute myeloblastic leukemia. *Blood* 1986; 68:1185–95.
3. Fialkow PJ, Singer JW, Raskind WH, Adamson JW, Jacobson RJ, Bemstein ID, et al. Clonal development, stem-cell differentiation, and clinical remissions in acute nonlymphocytic leukemia. *N Engl J Med* 1987; 317:468–73.
4. Keinanen M, Griffin JD, Bloomfield CD, Machnicki J, de la Chapelle A. Clonal chromosomal abnormalities showing multiple cell-lineage involvement in acute myeloid leukemia. *N Engl J Med* 1988; 318:1153–8.
5. Cadman EC, Capizzi RL, Bertino JR. Acute nonlymphocytic leukemia. *Cancer* 1977; 40:1280–96.
6. Layton DM, Mufti GJ. Myelodysplastic syndromes: their history, evolution, and relation to acute myeloid leukemia. *Br J Haematol* 1986; 53:423–36.
7. Bloomfield CD, de la Chapelle A. Chromosome abnormalities in acute nonlymphocytic leukemia: clinical and biologic significance. *Semin Oncol* 1987; 14:372–83.
8. Rowley JD, Alimena G, Garson OM, Hagemeister A, Mitelman F, Prigogina EL. A collaborative study of the relationship of the morphologic type of acute nonlymphocytic leukemia with patient age and karyotype. *Blood* 1982; 59:1013–22.
9. Islam A, Catovsky D, Goldman JM, Galton DAG. Bone marrow biopsy changes in acute myeloid leukemia: I. observations before chemotherapy. *Histopathology* 1985; 9:939–57.
10. Bennett JM, Catovsky D, Daniel MT, Flandrin G, Galton DAG, Gralnick HR, et al. Proposals for the classification of the myelodysplastic syndrome. *Br J Haematol* 1982; 51:189–99.
11. Lehmann EL. Nonparametrics: statistical methods based on ranks. San Francisco: Holden Day, 1975:5–23.
12. Mehta CR, Patel NR. A network algorithm for performing Fisher's exact test in rxc contingency tables. *J Am Stat Assoc* 1983; 78:427–34.
13. Hosmer DW, Lemeshow S. Applied logistic regression. New York: John Wiley and Sons, 1989:25–34.
14. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; 53:457–81.
15. Peto R, Peto J. Asymptotically efficient rank invariant test procedures (with discussion). *J R Stat Soc A* 1972; 135:185–206.
16. Tarone RE. Tests for trend in litt table analysis. *Biometrika* 1975; 62:679–82.
17. Cox DR. Regression models and life tables (with discussion). *J R Stat Soc B* 1972; 34:187–220.
18. Rai KR, Holland JF, Glidewell OJ, Weinberg V, Brunner K, Obrecht JP, et al. Treatment of acute myelocytic leukemia: a study of cancer and leukemia Group B. *Blood* 1981; 58:1203–12.
19. Keating MJ, Smith TL, Gehan EA, McCredi KB, Bodey GP, Spitzer G, et al. Factors related to length of complete remission in adult acute leukemia. *Cancer* 1980; 45:2017–29.
20. Foon KA, Gale RP. Controversies in the therapy of acute myelogenous leukemia. *Am J Med* 1982; 72:963–79.
21. Peterson BA, Bloomfield CD. Treatment of acute nonlymphocytic leukemia in elderly patients. *Cancer* 1977; 40647–52.
22. Sandberg AA. The chromosomes in human leukemia. *Semin Hematol* 1986; 23:201–17.
23. Kantarjian HM, Keating MJ, Walters RS, McCredie KB, Freireich

EJ. The characteristics and outcomes of patients with late relapse acute myelogenous leukemia. *J Clin Oncol* 1988; 6:232–8.
24. Curtis JE, Messner HA, Hasselback R, Elhakim TM, McCulloch EA. contributions of host- and disease-related attributes to the outcome of patients with acute myelogenous leukemia. *J* Clin *Oncol* 1984; 2:253–9.
25. Brito-Babapulle F, Catovsky D, Galton DAG. Clinical and laboratory features of de novo acute myeloid leukaemia with trilineage myelodysplasia. *Br J Hemat* 1987; 66:445–50.
26. Larson RA, Le Beau MM, Vardiman JW, Testa JR, Golomb HM, Rowley JD. The predictive value of initial cytogenetic studies in 148 adults with acute nonlymphocytic leukemia: a 12 year study. Cancer Genet Cytogenet 1983; 5:219–36.
27. Garson OM. Acute non-lymphocytic leukaemia. *Clin* Hematol 1980; 939–51.
28. Hiddemann W, Wormann B, Gohde W, Buchner T. DNA aneuploidies in adult p- nts with acute myeloid leukemia. Cancer 1986; 57:2146–52.
29. Fenaux P, Preudhomme C, Lai JL, Morel P, Beuscart R, Bauters F. Cytogenetics and their prognostic value in de novo acute myeloid leukaemia: a report on 283 cases. *Br J Hematol* 1987; 73:61–7.
30. Swirsky DM, de Bastos M, Parish SE, Rees JKH, Hayhoe FGJ. Features affecting outcome during remission induction of acute myeloid leukemia in 619 adult patients. *Br J Hematol* 1986; 64:435–53.
31. Mertelsmann R, Thaler HT, To L, Gee TS, McKenzie S, Schauer P, et al. Morphological classification, response to therapy, and survival in 263 adult patients with acute nonlymphoblastic leukemia. Blood 1980; 56:773–81.
32. Matsuo T, Goasquen J, Loy L, Bennet JM. Trilineage dysplasia in acute myeloid leukemia (AML): a study of 332 patients from an ECOG trial. Blood 1990; 76(Suppl 1):300.
33. Fearon ER, Burke PJ, Schiffer CA, Zehnbauer BA, Vogelstein B. Differentiation of leukemia cells to polymorphonuclear leukocytes in patients with acute nonlymphocytic leukemia. N *Engl J Med* 1986; 315:15–24.