To detect relapse acute myeloid leukemia (AML) treatment protocols have called for bone marrow exams every 2 to 4 months in remission. To investigate the effect of replacing this policy with one calling for marrows only when blood count is abnormal (platelets < 100,000, neutrophils < 1,000, circulating blasts > 5%, unrelated to prior chemotherapy), we reviewed the records of all 444 patients with AML whose disease recurred (≥5% marrow blasts unrelated to prior chemotherapy) for the first time between 1980 and 1995. The 375 patients with adequate follow-up were classified as (1) simultaneous - blood count abnormal when relapse noted without a normal marrow intervening between first abnormal count and relapse, 289 patients (77% of the 375), (2) marrow first - blood count normal when relapse noted, 60 patients (16%), or (3) blood first - a normal marrow intervened between first abnormal blood count and relapse, 26 patients (7%). Interval between marrow exams and blood counts did not differ in the three groups (a 25-patient sample of the 289 patient simultaneous group was analyzed as representative of this group) with marrows done at a median of once monthly and blood counts at a median of once weekly from complete remission (CR) date to relapse date. The three groups also had similar first CR duration, and pre-treatment cytogenetics. CR rates following salvage chemotherapy were 32% to 33% in the simultaneous and marrow first groups and 17% in the blood first group. We conclude that routine marrow exams for morphology are not needed in the great majority of AML patients in first CR.

Routine Bone Marrow Exam During First Remission of Acute Myeloid Leukemia

By Elihu Estey and Sherry Pierce

RELAPSE OF acute myeloid leukemia (AML) is considered to have occurred when the bone marrow contains ≥5% myeloblasts unrelated to recovery of normal hematopoiesis following chemotherapy. To detect relapse, AML treatment protocols have, therefore, called for bone marrow exams in remission. For example, a Cancer and Leukemia Group B (CALGB) study published in 1994 called for marrow aspirations at the completion of therapy, and then every 3 months for 1 year, every 5 months for 2 years, and finally, annually for at least 2 years. Recent studies of the Eastern Cooperative Oncology Group (ECOG) and the Australian Leukemia Study Group each called for marrow exams every 2 months for the first 2 years in remission, while a recent Southwest Oncology Group (SWOG) trial called for monthly marrows during three cycles of late intensification therapy and then marrows every 3 months for 2 years. The need for routine marrow exam to detect recurrence of AML was questioned by Müller and Sauter, who found that an abnormality in blood count occurred in the 3 months preceding marrow relapse in 97% of 69 episodes of relapse encountered in 40 patients, all of whom had completed chemotherapy. However, conversations with representatives of the ECOG (M. Tallman, 9/14/95), SWOG (F. Appelbaum, 9/14/95), and CALGB (R. Stone, 9/15/95) indicate that Müller and Sauter’s suggestion that the marrow be examined only if an abnormal blood count is detected has not been uniformly adopted. M.D. Anderson AML protocols also have continued to call for routine marrow aspirations every 1 to 2 months for the first 2 years in remission. Given these facts and increasing financial constraints, we have retrospectively reviewed the records of 444 patients with AML whose disease recurred, with the primary objective of determining the feasibility of replacing a policy of routine bone marrow follow-up exam with a policy mandating marrow exam only when blood count was abnormal. Secondary objectives were to compare characteristics and outcome of patients in whom (1) blood count was abnormal simultaneously with, but not before, detection of relapse, (2) relapse preceded abnormality in blood count, and (3) abnormality in blood count preceded relapse.

MATERIALS AND METHODS

The 444 patients represent all those with newly diagnosed AML whose disease entered complete remission as previously defined and then recurred for the first time between 1980 and 1995. Recurrence was defined as the presence of ≥5% blasts in the marrow unrelated to recovery of blood counts from a preceding course of chemotherapy. Sixty-nine of the patients (16%) were invaluable because disease relapse was noted in the absence of follow-up data regarding prior bone marrows or blood counts (53 patients, 12% of the 444) or because charts were unavailable (16 patients, 4% of the 444). The temporal relationship between marrow recurrence and an abnormality in blood count in the remaining 375 patients was classified as either (1) simultaneous — blood count was abnormal (defined below) when relapse was detected without a normal marrow intervening between detection of blood abnormality and relapse, (2) “marrow first” — blood count was normal when relapse was noted, or (3) “peripheral blood first” — abnormality in blood count preceded diagnosis of relapse, ie, a normal marrow intervened between the blood count abnormality and detection of relapse. An abnormality in blood count was defined as either a platelet count below 100,000/L, a neutrophil count below 1,000/L, or the presence of circulating blasts, in all cases unrelated to recovery from an immediately preceding course of chemotherapy, ie, occurring ≥1 month after such chemotherapy. The frequency with which marrow exams and blood counts were examined in the three groups, simultaneous, marrow first, and peripheral blood first is illustrated in Table 1, with results in the simultaneous group based on a random sampling of 25 patients. Considering the 101 patients in whom the frequency of marrow and blood exams was assessed from complete remission (CR) date to relapse date, the 25th, 50th, and 75th percentiles were 1, 1, and 2 months for marrow exams and 1, 1, and 2 weeks for blood exams. In the great majority of patients, blood counts and marrow exams were done at regular intervals. In a minority, those whose disease relapsed after a relatively long interval, the frequency of follow-up blood counts and marrows decreased with time. In
these cases we used the frequency in effect at around the time of relapse.

RESULTS

In 289 patients (77% of those evaluable), relapse was classified as simultaneous, in 60 (16%) it was classified as marrow first, and in 26 (7%) it was classified as peripheral blood first. Thus, in 84% of the evaluable patients (95% confidence limits, 78% to 88%) detection of disease relapse would not have been delayed had a policy of examination of marrow only when abnormal blood count was observed been in effect. Fifteen of the 60 patients in whom such a policy would have resulted in a delay in diagnosis of relapse (marrow first patients) began chemotherapy at diagnosis of relapse, thus affording no information as to time from relapse to development of abnormal blood count. Among the 45 marrow first patients in whom salvage chemotherapy was delayed until a blood count abnormality was observed, the median interval from relapse (ie, marrow with ≥5% blasts) to abnormal blood count was 4.5 weeks (25th percentile 2.5 weeks, 75th percentile 7.5 weeks, range, 1 to 20 weeks). Circulating blasts were the first abnormality detected in 47% of these marrow first patients, thrombocytopenia (ie, <100,000/µL) was first in 13%, neutropenia (ie, <1,000/µL) was first in 11%, and the remaining 29% had a combination of these abnormalities. In contrast, thrombocytopenia was the first abnormality detected in 77% of the 26 peripheral blood first patients, circulating blasts were detected first in 12%, thrombocytopenia and neutropenia were first in 8%, and monocytosis was first in 4%. Two of the 26 patients died, and two were begun on chemotherapy before a diagnosis of relapse (≥5% marrow blasts) could be made. The median interval from time when abnormal blood count thought unrelated to administration of chemotherapy (≥1 month after such administration) was first noted to diagnosis of relapse was 13 weeks (25th and 75th percentiles 5 and 18 weeks, range, 3 to 104 weeks) in the remaining 22 peripheral blood first patients.

Table 1 compares prerelapse characteristics of the simultaneous, marrow first, and peripheral blood first groups and the 53 members of the inadequate follow-up group in whom charts were available. Differences in frequency of marrow or blood exams between the simultaneous, marrow first, or peripheral blood first groups did not appear large enough to make it likely that classification into one of these groups was a function of how often blood and marrow exams were done. On the other hand, there was no seeming association between classification in a particular group and features such as duration of first remission (these appear relatively short to a large extent because patients who remain in remission were by definition excluded), cytogenetics, presence of an antecedent hematologic disorder before diagnosis of AML, age, or whether disease recurrence occurred during, or only following completion of, postremission chemotherapy (Table 1). Similarly, CR rates after first salvage chemotherapy for relapse were practically identical in the simultaneous and marrow first groups (84 of 266, 32%, and 19 of 57, 33%, respectively). This rate was lower, 3 of 18, 17%, in the peripheral blood first group (95% confidence interval for the true difference in CR rates between simultaneous and peripheral blood first patients [−.09, .38] and between marrow first and peripheral blood first patients [−.10, .42]). Among the 57 marrow first patients who received chemotherapy for first relapse, CR rates were 9 of 13, 69%, in those who began salvage chemotherapy at time of relapse versus 10 of 44, 23%, in those in whom salvage chemotherapy was delayed until blood count became abnormal (P = .003, Fisher exact test, 95% confidence interval for true difference in CR rates. (1.16, .71)). However, first remission duration was shorter in the delayed patients (P = .06, log-rank test), and it was impossible to ascertain other biases that could have influenced CR rates in the two categories of marrow first patients.

DISCUSSION

We found that in 84% of cases (95% confidence limits, 78% to 88%) an abnormality in blood count preceded, or was found simultaneously with, an excess of blasts (≥5%) in the marrow considered diagnostic of relapse. A qualitatively similar figure, 97%, was found by Müller and Sauter. Compared with these investigators, we had the opportunity to examine the records of almost 10 times as many patients, two-thirds of our patients were receiving postremission chemotherapy, whereas all of Muller and Sauter’s were off chemotherapy, recalling that, in general, a substantial number of relapses can be expected to occur while patients are receiving chemotherapy, and 22% of our patients were over age 65 years, whereas Swiss Group for Clinical Cancer Research (SAKK) patients (those examined by Müller and Sauter6) have at least in the past been limited to those under age 65 years.

Both our data and those of Müller and Sauter6 raise the question of whether routine marrow follow-up exams are needed in AML patients in first remission. Beyond noting that the data indicate that it is indeed feasible, on average, to dispense with such exams, we believe that a specific answer to the question depends on the clinical context in which it is raised, specifically on the therapy planned for the patient in the event of relapse. For older patients without a donor for a marrow transplant and who would receive conventional salvage chemotherapy, there appears to be little to be gained from being identified as one of the minority of patients in the marrow first group. In contrast, patients who would receive an allogeneic transplant at relapse have been shown to benefit if relapse can be detected earlier; here a policy of routine marrow exam could be considered appropriate.

Several other points should be made. First, blood counts and marrows in our patients were obtained at particular intervals (Table 1), and, although intervals were similar in simultaneous, bone marrow first, and peripheral blood first patients, the frequency with which blood counts and marrows are procured could influence how often a policy of marrow exam only when abnormal blood count is noted could successfully replace the traditional policy. Second, salvage chemotherapy produced a higher CR rate in bone marrow first patients who began treatment when the marrow indicated relapse, but the blood count was still normal than in bone marrow first patients who began chemotherapy only when an abnormality in count was observed. However, there is no
assurance that the two groups of bone marrow first patients differed only as to timing of salvage chemotherapy; for example the patients who began treatment later had shorter first remissions, a feature generally associated with poorer response to salvage therapy.\(^\text{10}\) Only a trial randomizing bone marrow first patients to immediate or delayed chemotherapy could address this issue. Such a trial would be difficult to organize, given our data suggesting only a small minority of patients will be bone marrow first if blood counts are monitored weekly-semiweekly. Finally, our data obviously apply only to morphologic monitoring of marrow. Fluorescent in situ hybridization (FISH) or polymerase chain reaction (PCR) techniques may permit earlier detection of relapse than is possible using morphology,\(^\text{11}\) thus reducing the relevance of our findings; this is particularly true in patients with acute promyelocytic leukemia (APL).\(^\text{12}\)

There appears to be no evidence that simultaneous, bone marrow first, and peripheral blood first groups differ (Table 1), with the possible exception of the lower CR rate after salvage chemotherapy in the peripheral blood first group, despite similarities in first remission duration in the three groups. Acknowledging that this finding could be artifactual as discussed above, the result might suggest that use of marrow criteria for relapse overestimates first CR duration in peripheral blood first patients, who are, thus, a poorer prognostic group than would appear if marrow criteria are employed. However, before failure of blood counts to recover can be made a criterion for relapse, it would be necessary to determine the proportion of patients whose counts remain low at various times after chemotherapy who, in fact, proceed to marrow relapse, a difficult logistical undertaking for us, at least retrospectively. Additionally, before abnormal blood counts were used to define relapse, a randomized trial comparing treatment at detection of abnormal count versus treatment at detection of traditional, ie, marrow, relapse might be of use (although again logistically difficult, as our data suggest that the interval between the two events can be long).

In conclusion, our data suggest that bone marrow exams for morphology are superfluous in \(\approx80\%\) of patients (simultaneous and peripheral blood first groups) with AML in first CR provided blood counts are obtained weekly-semiweekly. The decision to forego routine marrow exams should, however, be individualized, particularly bearing in mind the therapy planned at relapse.

REFERENCES


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