One Hundred Twenty-Five Adult Patients With Primary Acute Leukemia Autografted With Marrow Purged by Mafosfamide: A 10-Year Single Institution Experience


A total of 125 acute leukemia adult patients were autografted with bone marrow (BM) purged by mafosfamide (ASTA Z) during the period of January 1983 to January 1993. The median follow-up period was 64 months (range, 3 to 126). There were 84 acute myeloblastic leukemias (AMLs) and 41 acute lymphoblastic leukemias (ALLs). At time of autologous BM transplantation (ABMT), 64 AMLs were in first complete remission (CR1), and 20 were in second CR (CR2); 35 ALL were in CR1, and 6 were in CR2. The median age of the patients was 33 years (range, 16 to 55). The median interval between achieving CR and autografting was 5 months (range, 1.3 to 23). The pretransplant regimen consisted of cyclophosphamide (120 mg/kg) and total body irradiation (TBI) followed by ABMT with BM purged by mafosfamide, a directly active, in the past 2 decades, several teams including ours have reinforced the view that ABMT is one approach to improve the outcome of adult patients with acute leukemia. The initial richness of the BM at collection and the timing of the transplant are important predictive factors for the outcome. © 1994 by The American Society of Hematology.

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Table 1. Characteristics of the 125 Patients With Acute Leukemia and Their BM Grafts Purged by Mafosfamide

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>AML</th>
<th>ALL</th>
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| Patient
| characteristics |
| No. of patients| 84  | 41  |
| Sex ratio M/F  | 50/34 | 29/13 |
|                | M4 + M5/other: | 26/68 |
| No. of patients in CR1* | 64 | 35 |
| Age (yr)       | 36 (16-53) | 29 (17-55) |
| Interval CR1-ABMT (d) | 150 (4-184) | 143 (44-523) |
| Follow-up (mo) | 62 (3-126) | 78 (8-125) |
| Characteristics of the BM purged with mafosfamide* |
| CFU-GM (10^5/kg) before purging | 4.8 (0.55-32.5) | 6 (0.8-33) |
| CFU-GM (10^5/kg) after purging | 0.019 (0.018) | 0.032 (0.1.26) |
| CFU-GM fraction recovery postpurging (%) | 0.36 (0.27) | 0.41 (0.13) |
| Dose of mafosfamide used for purging at adjusted levels (µg/mL) | 71 (15-160) | 95 (35-140) |

* All values are given as median and range (units as indicated within parenthesis).
† ALL population is significantly younger than the AML population (P = .04).
‡ Statistically significant, P = .02.

ALL patients, 3 had a Philadelphia chromosome, and 1 had a t(4;11) translocation. Using the tentative cytogenetic prognosis classification of Jorge et al., 14 (44%) of those with clonal abnormalities would be in the high-risk and 26 (81%) in either the intermediate- or high-risk categories.

The nature of induction and consolidation chemotherapies administered to patients with AML in the pretransplant period varied, because the majority came to our institution already in CR having been sent by referral centers. All patients in CR received 2 to 3 consolidation courses of cytosine arabinoside (ARA-C) (conventional) + asparaginase (AMS) alternatively with ARA-C (conventional) and etoposide. The median interval from CR to ABMT was 5 months.

Patients with ALL were treated according to the French national protocol. After achievement of CR, they also received 2 to 3 courses of consolidation therapy. 15 Except for nonhypercellular AML French-American-British (FAB) 1, 2, and 3, before ABMT, all patients received central nervous system (CNS) prophylaxis consisting of 6 weekly intrathecal administrations of methotrexate (15 mg total dose) + methyl prednisolone (20 mg) and cranial irradiation at 15 Gy. After the ABMT, patients with a previous history of leukemia involving the CNS received additional intrathecal injections of methotrexate for a total of 12 monthly administrations. Table 1 summarizes the principal characteristics of the 125 patients.

Collection of BM, incubation with mafosfamide, and cryopreservation. All patients underwent BM collection while in CR. BM collected was divided into two parts, (1) a back-up BM corresponding to 0.75 x 10^6 nucleated BM cells per kg that was saved and directly cryopreserved and (2) a BM treated with mafosfamide to be used for ABMT.

To purge the BM with mafosfamide, we used 2 techniques. In a first period from January 1982 to January 1990, we adjusted the doses of mafosfamide to the individual sensitivity of the normal CFU-GM in each patient in an effort to reach the highest tolerable dose that would achieve a maximum antileukemic activity without jeopardizing BM engraftment. This dose was defined as the CFU-GM LD 95 on buffy-coat BM cells, sparing 5% ± 5% CFU-GM. 16,17 A total of 95 patients had their BM treated according to this technique.

In a second period from January 1990 to January 1993, 30 patients had their BM Ficoll-Hypaque separated; the mononuclear cell fraction was adjusted to a final concentration of 10^7/mL and treated with a constant dose of 50 µg/mL of mafosfamide. Whatever the dose, the BM suspension was incubated with mafosfamide for 30 minutes in a water bath at 37°C and then immediately cooled and centrifuged at 4°C to block the action of the drug abruptly. After 2 washes, the BM cells were then resuspended in irradiated autologous plasma (40 Gy) and TC 199 medium and finally frozen with 10% dimethylsulfone in Teflon-Kapton DF 1000 Gambio bags (Gambro Dialysatoren, GMBH, Germany) using a Nicool 316 programmed biologic freezer (CFPO, Sassenage, France), following our freezing technique as previously published. 18-14 The purged BM was then stored in the gas phase of liquid nitrogen at a temperature constantly below −190°C. Cell counts and CFU-GM evaluations were performed at all steps of the procedures. The numbers of residual progenitor cells after incubation with mafosfamide were known for each individual patient before ABMT.

High-dose consolidation and transplantation. We used the standard pretransplant consolidation treatment consisting of CY (60 mg/kg in two doses, along with 2-mercaptoethane sodium sulfonate at 60% of the dose of CY) followed by total body irradiation (TBI). Two modalities of TBI were used, single TBI at the total dose of 10 Gy with lung shielding at 8 Gy and fractionated TBI (FTBI) in 6 fractions of 200 cGy over 3 days with lung shielding at 9 Gy. Patients treated until June 1985 all received single-dose TBI. After June 1985, ALL patients received FTBI.

At the time of ABMT (day 0), each bag was thawed and infused through a central venous catheter at a rate of 10 to 15 mL per minute. Supportive measures during the period of aplasia preceding engraftment followed our usual standards. After ABMT, no maintenance chemotherapy was used.

Hemopoietic progenitors. CFU-GM were cultured in agar according to the technique of Pike and Robinson. 15 CSA was supplied by 10% human placental conditioned medium produced according to the method of Schlunk and Schleyer. The results were expressed in terms of the number of colonies per kilogram of body weight. CFU-GM were evaluated at all steps, ie, on BM collected in surgery room, before and after purging, and before and after cryopreservation. The CFU-GM fraction recovery postpurging was obtained by dividing the CFU-GM/kg remaining after treatment with mafosfamide (CFU-GM2) by the initial CFU-GM/kg pretreatment value (CFU-GM1).

Analysis of data and statistical methods. Statistical analyses were performed using the BMDP program. The statistical differences in percentage were determined with the χ² test or the Fisher’s exact test.

To study the kinetics of recovery of hemopoiesis, the day of engraftment was defined as the first day with a persistent blood cell count above a predefined level, ie, 1 x 10^9/L for leukocytes, 0.5 x
diagnosis, status at transplant, sex, age at time of transplant, interval from CR to ABMT. A second multivariate analysis stratified on diagnosis was performed to evaluate the influence of the same variables on the probability of engraftment. For all comparisons, quantitative variables were dichotomized either on logical ground or systematically using median value.

RESULTS

Purge with mafosfamide and hematopoietic progenitors. Table 1 indicates the major characteristics of the 125 transplanted BMs purged with mafosfamide. Patients with AML received BM containing $0.02 \times 10^6$ CFU-GM/kg (range, 0 to 1.78), and patients with ALL received $0.03 \times 10^6$ CFU-GM/kg (range, 0 to 1.26). BM cells received by 22 AML and 11 ALL patients did not contain detectable CFU-GM. The CFU-GM LD95 dose of mafosfamide used was significantly ($P = .02$) higher in ALL than in AML ($95 \mu g/mL$ and $71 \mu g/mL$, respectively), possibly indicating a higher sensitivity of CR CFU-GM in AML.

Comparisons of BM treated at adjusted levels with BM purged with a constant dose of mafosfamide (Table 2) showed two differences in AML, lower CFU-GM counts ($P = .02$) and patients with no residual CFU-GM ($P = .006$) when purged with a constant dose.

Engraftment and kinetics of recovery of hematopoiesis. The role of factors potentially influencing engraftment was evaluated according to (1) the probability to engraft and (2) the time necessary to recover hematopoiesis in patients successfully engrafted. In our analysis, 83% AML patients and 88% ALL patients were engrafted successfully.

In patients with AML, we observed engraftment by leukocytes by day 29 (range 12 to 69), by neutrophils by day 30 (range, 12 to 153), and by platelets by day 90 (range, 19 to 850). In patients who received BM containing 0.02 $\times 10^6$ CFU-GM/kg (range, 0 to 1.78), and patients with ALL received 0.03 $\times 10^6$ CFU-GM/kg (range, 0 to 1.26). BM cells received by 22 AML and 11 ALL patients did not contain detectable CFU-GM. The CFU-GM LD95 dose of mafosfamide used was significantly ($P = .02$) higher in ALL than in AML ($95 \mu g/mL$ and $71 \mu g/mL$, respectively), possibly indicating a higher sensitivity of CR CFU-GM in AML.

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In patients with AML, we observed engraftment by leukocytes by day 29 (range 12 to 69), by neutrophils by day 30 (range, 12 to 153), and by platelets by day 90 (range, 19 to 850). In patients with ALL, we observed engraftment by leukocytes by day 20 (range, 13 to 136), by neutrophils by day 20 (range, 13 to 136), and by platelets by day 37.5 (range, 15 to 120). Therefore, engraftment occurred more rapidly in ALL than in AML ($P = .0004$ for neutrophils; $P = .003$ for platelets).

The multivariate analysis (Table 3) was stratified on diagnosis. Four factors significantly affected the kinetics of recovery of hematopoiesis. (1) Older age of the patients, (2) purging at a constant dose of mafosfamide, (3) autografting in CR2, and (4) a longer interval from CR to transplant were associated with slower recoveries for both neutrophils and platelets. There was a trend for a more rapid recovery of neutrophils in patients receiving the richer BM evaluated in CFU-GM/kg prepurging ($P = .06$).

In 22 AML and 11 ALL patients, no CFU-GM was detectable after in vitro treatment of the BM with mafosfamide. The probability of AML patients to engraft tended to be lower for both neutrophils ($P = .09$) and platelets ($P = .11$). A total of 4 AML and 1 ALL patients died from early toxicity and no engraftment. All other patients were engrafted with
recoveries of neutrophils, leukocytes, and platelets within 38.5 days (range, 15 to 153), 27 days (range, 12 to 57), and 201 days (range, 70 to 820), respectively, in AML and within 22 days (range, 15 to 52), 20 days (range, 13 to 52), and 60 days (range, 23 to 93), respectively, in ALL. Platelet recovery in these AML patients was significantly longer when compared with that of patients engrafted with BM containing detectable CFU-GM.

Toxicity and causes of death. Complications during the course of ABMT mainly consisted of infections of various origin, bacterial (58% of the patients), viral (38%), and fungal (22%). Twenty-nine patients developed interstitial pneumonitis. Altogether, cytomegalovirus was responsible for 7 infections, none of which was fatal. During transplant, 9 patients (AML, 7; ALL, 2) developed liver veno-occlusive disease (VOD). Two of these patients died of VOD, whereas this evolution contributed to death in 1 patient. One patient experienced a Cy-induced hemorrhagic cystitis. After discharge, in the late transplant period, 1 patient was found to be human immunodeficiency virus-positive 6 months after transplant in 1987. He is presently alive under AZT therapy. As of today, 21 cataracts have been diagnosed and treated appropriately in 15 AML and 6 ALL patients, 17 of whom had received single-dose TBI and 4 of whom received FTBI. Overall, 20 patients died as a consequence of transplant-related toxicity, including nonengraftment or poor engraftment. The primary causes of death were bacterial infection (6 patients) including septic shock (3 patients), interstitial pneumonitis (4 patients), viral infection (4 patients), pneumonitis (3 patients), liver VOD (2 patients), and hepatitis (1 patient). Although in CR more than 1 year after ABMT, four of these patients died as follows: two patients developed cirrhosis with portal hypertension at 13 and 21 months; a third patient had viral encephalitis at 16 months; and the fourth patient, although in CR for more than 7 years had a meningococcus sepsis occurring as a complication of a splenectomy performed at the time of the diagnosis at the referring center. This patient explains the drop in the LFS curve at 7 years.

LFS, relapse rate, and TRM. Of the 125 patients, 20 died from toxicity (see above), 36 relapsed, and 69 are presently alive in CR. In the global population, with a median follow-up of 64 months (range, 3 to 126), the LFS was 54% ± 5% and the RI 33% ± 5% at 8 years.

Patients with AML had an LFS of 52% ± 6%, with 58% ± 7% for those autografted in CR1 and with 34% ± 11% for those in CR2 (Fig 1). The corresponding values for RI were 25% ± 6% in CR1 and 48% ± 12% in CR2. Patients with ALL had an LFS of 57% ± 8% (56% ± 8% when considering only those autografted in CR1; see Fig 2). Of the 6 patients transplanted in CR2, 4 are presently in CR. The probability of relapse and the TRM were 37% ± 8% and 10% ± 5%, respectively. Table 4 summarizes the results of the univariate analysis. There was no difference when comparing AML and ALL for LFS, RI, and TRM. Similarly, there was no difference when comparing the overall relapse rates in CR1, but late relapses were an almost exclusive feature of ALL because 8 of 30 ALL but only 2 of 49 AML patients (autografted in CR2) relapsed beyond 1 year posttransplant, thus giving a late RI at 8 years of 31% ± 10% for ALL versus 4% ± 3% for AML (P = .004). By multivariate analysis, 2 factors were found to influence LFS, relapse rate, and TRM (Table 5). The first one, which concerned the characteristics of the graft itself (namely, the initial richness of the BM before purging), was associated with LFS and TRM. Figure 3 shows the LFS and TRM of patients receiving BM doses above the median value, as compared with those receiving lower doses. Patients of the higher dose group had a better LFS (64% ± 7% v 44% ± 7%; P = .022) and a lower TRM (4% ± 3% v 34% ± 8%; P = .003). The second factor, the interval from CR to transplant was correlated with RI. Patients grafted within 5 months from CR had a lower RI (24% ± 6% v 40% ± 7%; P = .04).

**DISCUSSION**

In this article, we report on 125 adult patients with acute leukemia autografted with BM treated in vitro by mafosfamide. At 8 years, the LFS is 54% ± 5%, and the RI 33% ± 5%. We found no difference in survival curves between AML and ALL patients with the exception of late relapses occurring almost exclusively in ALL patients. The richness
of the BM before purging and a shorter interval from CR to ABMT were correlated with a better outcome. The engraftment was significantly slower in AML than in ALL. A younger age, an ABMT performed in CR1, the use of an adjusted dose of mafosfamide, and a shorter interval from CR to ABMT influenced engraftment favorably. This work is a comprehensive review of our 10-year experience with ABMT since January 1983, when we started to consolidate patients with acute leukemia in remission by the mean of ABMT with the same standard preparative regimen (CY + TBI) in use for allogeneic BMT. We will review the three main topics derived from our results, engraftment, survival curves, and potential role of purging.

Regarding engraftment, we reported on an intermediate group of patients (slow kinetics of recovery for both neutrophils and platelets in AML as compared to ALL). The finding is confirmed here in a much larger series of patients with a recovery of neutrophils on day 30 in AML versus day 20 in ALL and of platelets on day 90 versus day 37, respectively. Several teams have reported the same observation with unpurged BM, and slow kinetics of engraftment are now recognized as a characteristic of ABMT in AML. Many groups including ours have failed to correlate this difference between AML and ALL to any factor other than the nature of the leukemic disease, per se; it has been suggested that AML, which originates as a clonal disease on an earlier multipotent stem cell, is associated with a residual normal stem cell pool that is more reduced and/or more damaged than that in ALL and, therefore, results in a slower engraftment. In the present study, we identified pronostic factors for rapid engraftment, ie, (1) younger age, (2) ABMT in CR1 (3) purging at levels individually adjusted, and (4) early transplantation. Indeed, AML patients with all these characteristics would have a relative risk (RR) of 3.3 for quicker engraftment on neutrophils and of 5 for quicker engraftment on platelets. There also was a trend for faster engraftment on neutrophils in patients receiving the higher doses of BM (CFU-GM/kg prepurging). These observations may reflect a reduced stem cell pool with increasing age and a higher toxicity because of chemotherapy in patients transplanted late and/or in CR2. Whether BM treatment with mafosfamide further delays engraftment, a potential hazard of purging, is still a matter of debate. Observations compiled from small series and an unpublished analysis from the European Cooperative Group for Bone Marrow Transplantation (EBMT) have suggested that it may indeed be so in AML but not in ALL. However, in the absence of any existing randomized study comparing patients autografted with purged and unpurged BM, a definitive answer is not possible. The present analysis shows for the first time that patients engrafted with BM purged at a constant dose have a considerably higher probability for slow engraftment than those receiving BM purged at an adjusted dose. However, this did not translate into a better outcome in terms of better LFS and lower TRM, probably because of the appropriate supportive therapy. However, the slow kinetics of engraftment of AML patients is a matter of concern, because it has direct implications on both the total duration of hospitalization and the overall cost of the procedure.

Regarding survival curves, we report in CR1 an LFS and relapse rate at 8 years of 58% and 25% for AML and 56% and 37% for ALL and, in CR2, an LFS and relapse rate at 4 years of 34% and 48% for AML. It is important to notice that, in patients autografted in CR1, we had no relapse after 1 year in AML, which is in contrast to ALL in which late relapses occurred up to 78 months. When we initially designed our protocol in 1982, it was somewhat unique in several aspects. ABMT, per se, was experimental and its use in acute leukemia was severely criticized especially as early as CR1; BM purging, per se, and further purging with CY derivatives had not been evaluated in humans. In the 10 years covered by this study, important information became available that has consistently strengthened our approach so that we never modified our protocol. Others, usually with a more limited follow-up, reported on smaller series with similar results for AML using BM purged by CY derivatives. Results from the European Registry show, at 7 years, an LFS of 55% and an RI of 29% in CR1, an LFS of 34% and an RI of 54% in CR2. For ALL, on the other hand, we are not aware of comparable studies, because purging was
usually performed with monoclonal antibodies rather than mafosfamide.35-39 In our series, we report two new independent factors influencing the outcome. The first one is the initial richness of the BM before purging. Patients receiving the highest dose of BM (greater than $5.15 \times 10^4$ CFU-GM/kg) had a lower risk of TRM and a higher chance for cure. At present, the explanation is unclear. As indicated above, patients receiving the richer BM tended to engraft faster on neutrophils, but this had no impact on the outcome. It may be that ability to collect rich BM reflects a high-quality CR and, therefore, a good prognosis indicator. Alternatively, one may hypothesize the intervention of a stem cell competition effect, whereby an expanded normal stem cell pool would express a growth advantage and/or a higher resistance (eg, to inhibitors of leukemic origin), when faced by a minimal residual tumor population. Such a mechanism has been recently suggested to explain achievement of CR in patients in relapse of leukemia after allogeneic BMT, after administration of granulocyte colony-stimulating factor.40 Our finding would support collecting and infusing the highest possible dose of BM and might even question the routine putting aside of a back-up BM. The second factor influencing outcome, namely the timing of ABMT, had an impact on relapses with a lower incidence in patients autografted earlier. The explanation is uncertain; however, it may be proposed that patients reaching ABMT earlier were in a better clinical and hematologic condition and, in a way, selected for good prognostic criteria pertaining to the leukemia itself. This hypothesis may be supported by the fact that BM before (P = .07) and after (P = .07) purging in this group of patients tended to be richer.

Efficiency of purging is still under debate. We introduced mafosfamide for in vitro purging of the graft after the observation by the Baltimore team that CY derivatives were able to eliminate residual BM leukemic cells in the Brown Norway myelocytic leukemia rat model.24 This decision concluded a first period during which we set up our cryopreservation technique and storage facilities8,14 and demonstrated the feasibility of ABMT in patients with end-stage acute leukemias.10,41,42 This established the relationship of the dose of CFU-GM progenitors in the graft with both the cryopreservation efficiency 18,43 and the kinetics of engraftment. Because we observed a wide range of patients’ sensitivity to mafosfamide, we defined the CFU-GM LD 95 on buffy-coat cells as the highest possible dose to use for effective antileukemic activity. This dose resulted in sparing enough normal stem cells for successful engraftment. Because we planned a European study for evaluation of purging, we simplified the technique for BM purging. In a second period, after a preclinical stage, we switched to BM purged at a constant dose.45 In AML, in addition to animal preclinical models29,31 clinical data also have been progressively accumulated in favor of purging with CY derivatives. The Baltimore team has provided indirect evidence in favor of purging by reporting that in vitro treatment of the BM as assessed by the elimination of CFU-GM colonies was associated with a significant decrease in relapse.26 Later, the same team correlated the sensitivity to 4-hydroperoxycyclophosphamide (4-HC) of clonogenic leukemia cells grown in remission with the posttransplant outcome.27 Analysis of EBMT32 has shown a lower relapse rate with purged BM that is

| Table 4. Factors Influencing LFS, RI, and TRM: Univariate Analysis |
|--------------------------|----------------|----------------|----------------|----------------|
| Diagnosis                | LFS | P | RI | P | TRM | P |
| ALL                      | 52 ± 6 | 63 | 30 ± 5 | 75 | 25 ± 6 | .19 |
| AML                      | 48 ± 11 | 42 ± 9 | 10 ± 5 |     |
| Sex                      |     |     |     |     |     |     |
| Male                     | 48 ± 7 | 35 ± 7 | 22 ± 6 | .87 |
| Female                   | 54 ± 7 | 36 ± 8 | 16 ± 6 |     |
| Age                       |     |     |     |     |     |     |
| ≤33                      | 53 ± 8 | 40 ± 7 | 8 ± 3 | .02 |
| >33                      | 49 ± 8 | 30 ± 7 | 31 ± 8 |     |
| WBC count (10^9/L) at diagnosis ≥16.2 | 56 ± 10 | .73 | 26 ± 7 | 14 ± 11 | .08 |
| ≤16.2                    | 55 ± 9 | 41 ± 8 | 5 ± 3 |     |
| Status at transplant     |     |     |     |     |     |     |
| CR1                      | 54 ± 6 | .13 | 32 ± 9 | 18 ± 5 | .54 |
| CR2                      | 42 ± 10 | 44 ± 10 | 25 ± 10 |     |
| Interval between diagnosis and CR1 (pts in CR1) ≤46 d | 44 ± 9 | .36 | 43 ± 9 | 19 ± 9 | .45 |
| >46 d                    | 62 ± 7 | .23 | 7 | 20 ± 6 |     |
| Interval between CR and ABMT ≤150 d | 61 ± 7 | .053 | 24 ± 6 | 03 ± 19 | .67 |
| >150 d                   | 42 ± 7 | .46 | 8 | 20 ± 6 |     |
| CFU-GM before purging (10^9/kg) ≤5.15 | 41 ± 7 | .39 | 8 ± 5 | 27 ± 9 | .003 |
| >5.15                    | 63 ± 6 | 38 ± 6 | 7 ± 3 |     |
| Purging method            |     |     |     |     |     |     |
| Adjusted                  | 52 ± 10 | .37 | 11 | 17 ± 7 | .70 |
| Constant                  | 52 ± 6 | .70 | 34 ± 5 | .83 | 19 ± 10 | .70 |
| Dose of mafosfamide (adjusted only) ≤78 µg/mL | 61 ± 7 | .22 | 6 | 21 ± 7 | .98 |
| >78 µg/mL                 | 42 ± 8 | .47 | 8 | 16 ± 5 |     |
| CFU-GM after purging (10^9/kg) ≤0.02 | 45 ± 8 | .39 | 8 | 13 ± 6 | .14 |
| >0.02                    | 57 ± 7 | .33 | 6 | 15 ± 6 |     |
| CFU-GM recovery postpurging ≤0.36% | 50 ± 8 | .86 | 35 ± 8 | 58 ± 20 | .30 |
| >0.36%                   | 52 ± 6 | .36 | 8 | 19 ± 7 |     |
| Time to ANC >0.5 x 10^9/L ≤26d | 65 ± 7 | .65 | 33 ± 7 | 77 ± 12 | .08 |
| >26d                     | 51 ± 10 | .34 | 9 | 19 ± 9 |     |
| Time to leukocytes >10^9/L ≤25d | 59 ± 8 | .36 | 7 | 82 ± 3 | .10 |
| >25d                     | 54 ± 8 | .31 | 7 | 21 ± 9 |     |
| Time to platelets >50 x 10^11/L ≤65d | 67 ± 10 | .39 | 8 | 44 ± 0 | .32 |
| >65d                     | 74 ± 9 | .20 | 7 | 8 ± 7 |     |

Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count.

| Table 5. Prognostic Factors Correlated to LFS, RI, and TRM in 125 Patients With Acute Leukemia Autografted Using BM Purged by Mafosfamide: Multivariate Analyses |
|--------------------------|----------------|----------------|----------------|----------------|
| LFS                      | P | RI | P | TRM | P |
| CFU-GM/kg (10^9) before purging >5.15 v ≤5.15 | 0.57 | .045 | 0.21 | .003 |
| Interval from CR to ABMT >5 mos v ≤5 mos | 2.05 | .03 |

Comparisons apply to values greater than or equal and inferior to median values in each population.
more pronounced in patients transplanted early and in slow
remitters, two situations that were interpreted as correspond-
ing to a higher probability for persistence of a higher residual
tumor load. More recent analyses have indicated a possible
higher probability of cure with purged rather than unpurged
BM (91% vs 80%) for patients autografted in CR1 post-TBI
who did not relapse at 1 year. Different relapse patterns were
observed in the two populations, with late relapses until 32
months occurring only in the group receiving unpurged BM.
Recently, Brenner et al.20 have been able to mark the un-
purged autograft by transferring the Neomycin-resistance
gene in 12 ABMTs for AML. In the 2 cases where a relapse
occurred, they subsequently showed the presence of the
marker in leukemic cells, and in leukemic colonies grown
in culture. This observation suggests that, at least in certain
cases, the graft itself contributes to the relapse. In contrast
to AML, in ALL, evidence in favor of in vitro treatment
with CY derivatives has only come from in vitro studies on
cell lines, and there has not been any demonstration of bene-
fit in terms of lower relapse rate or higher LFS in human
clinical situations.

In the 10 years covered by this study, the potential benefit
of ABMT over conventional chemotherapy (CT) or com-
pared with allogeneic BMT has been questioned. Compari-
sions of therapeutic strategies using CT alone with those
including allogeneic BMT or ABMT have been attempted
through both retrospective and prospective studies. The
available data mainly concern AML. They essentially indi-
cate similar results for allogeneic and autologous BMT with
unpurged BM46 and a significant advantage for BM trans-
plantation over CT.47 The only trial presently in progress
comparing ABMT using BM purged with a CY derivative,
4-HC, to allogeneic BMT and CT is the ECOG trial.48 A
comparison between autologous and allogeneic BMT should
take into account the feasibility of both techniques. In a
recent study, Bernan et al.54 reviewing 350 patients with
AML treated in a single institution, indicated that 9% of this
global population actually underwent an allogeneic BMT.
In a similar study in our institution on a cohort of 124 patients
admitted at initial diagnosis, 60-years-old or younger, the
fraction of patients actually autografted was 36%.50 There-
fore, our results strongly suggest that ABMT in AML can
be offered to more patients than allogeneic BMT, and it is
associated with a high LFS, even though it is still unclear
whether the most recent improvement of CT might bring
similar results. In contrast to AML, ALL does not presently
enable a comparative evaluation of various treatment modal-
ities with or without ABMT.

Our experience takes advantage of having the longest ex-
isting follow-up time. We conclude that ABMT with BM purged by mafosfamide is feasible for both AML and ALL
in a large fraction of patients and is followed by a high LFS.
The results of multivariate analyses suggested collecting as
much BM as feasible and performing ABMT preferentially
in patients in CR1. Research programs in our institution are
presently aiming at speeding up engraftment in AML either
with the use of agents protecting normal stem cells in vitro
during purging or with cytokines administered in vivo post-
transplant.

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