



## Autologous blood stem cell transplantation for acute myeloblastic leukemia in first complete remission. Intensification therapy before transplantation does not prolong disease-free survival

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### ABSTRACT

*Background and Objective.* To compare the clinical results of two consecutive therapeutic protocols including autologous blood stem cell transplantation (ABSCT) for patients with *de novo* acute myeloblastic leukemia (AML) in first complete remission (CR1).

*Design and Methods.* Between November 1989 and January 1997, 50 patients with AML in CR1 underwent ABSCT using two consecutive protocols. In the first one (Group A, 25 patients) peripheral blood stem cells (PBSC) were collected after induction and consolidation chemotherapy courses, and ABSCT was performed immediately thereafter. In the subsequent 25 patients (Group B), PBSC were collected after consolidation alone, and a further chemotherapy course with intermediate dose cytarabine (Ara-C 1 g/m<sup>2</sup>/12h × 3 days) and mitoxantrone (12 mg/m<sup>2</sup>/d × 3 days) was administered as early intensification. The conditioning regimen consisted of busulfan (16 mg/kg) and cyclophosphamide (200 mg/kg) in every case.

*Results.* Hematopoietic engraftment was slightly quicker in Group B, with median times to reach 0.5 × 10<sup>9</sup> neutrophils/L and 20 × 10<sup>9</sup> platelets/L being 13 and 12 days in Group A and 12 and 11 days in Group B, respectively. There were three graft failures (8%) (2 in Group A and 1 in Group B) and three transplant-related deaths (8%) (2 in Group A and 1 in Group B). No significant differences were observed between the groups in terms of relapse (64% at 4-years in Group A and 81% in Group B). Likewise, the actuarial 4-year disease-free survival (DFS) was not significantly different between the two groups (32% v 18%).

*Interpretation and Conclusions.* Our study confirms that AML patients in CR1 receiving ABSCT have rapid engraftment with low mortality. However, autologous transplants with PBSC collected after consolidation chemotherapy were still associated with a high rate of relapse (RR). This RR was not apparently reduced by the administration of intermediate dose Ara-C before transplantation.

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Key words: autologous blood cell transplant, acute myeloblastic leukemia, first remission

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Several series have demonstrated that peripheral blood stem cells (PBSC) can be collected from patients with acute myeloblastic leukemia (AML) in first complete remission (CR1) using chemotherapy alone for mobilization.<sup>1-5</sup> Likewise, we and others have confirmed the feasibility of performing an autologous blood stem cell transplantation (ABSCT) in AML patients.<sup>1-5</sup> Rapid post-transplantation hematopoietic recovery resulting in low morbidity and mortality rates is the main advantage of the procedure. However, as in autologous bone marrow transplant (ABMT), leukemic relapse remains the major problem of this therapeutic strategy. In our previously reported series, 24 patients with AML in CR1 received BUCY conditioning regimen followed by ABSCT with PBSC collected after induction and after consolidation.<sup>4</sup> In that series, the actuarial disease-free survival (DFS) and actuarial risk of relapse at 30 months were, at that time, 35% and 60%, respectively.<sup>4</sup> In order to reduce the relapse rate, we modified our original schema, trying to decrease the minimal residual disease in the inoculum as well as in the patient. For that, PBSC collections were performed only after consolidation, and an additional intensification chemotherapy course with intermediate dose cytarabine (Ara-C) and mitoxantrone (MTZ) was added after consolidation.

In this paper, we report the outcome of the largest series of AML patients in CR1 undergoing ABSCT from a single institution. The major aim of our study was to compare the long-term outcome of the previously reported patients<sup>4</sup> with that of 25 patients treated according to the new protocol. According to our results, the new therapeutic approach failed to give any significant benefit in terms of DFS or relapse rate.

### Design and Methods

#### Study patients

From November 1989 to January 1997, every patient 14 years of age or older with *de novo* AML diagnosed at our institution was eligible for the study. Patients with acute promyelocytic leukemia or secondary leukemia were excluded. The protocol was primarily designed for patients aged up to 60

years, though older patients could be entered if they were considered suitable for intensive therapy. Up to December 1991, PBSC collections were planned after induction and after consolidation chemotherapy, and the ABSCT was performed immediately post-consolidation (Group A). In January 1992, we started a new therapeutic protocol of performing PBSC collections only after consolidation, and administering an additional intensification chemotherapy course before transplantation (Group B).

#### *Pre-transplant treatment*

One hundred and thirty-nine of 141 consecutive patients with AML diagnosed at our institution were eligible for induction (54 in Group A and 85 in Group B). Two patients were unevaluable due to death before starting treatment (1 case) or very poor clinical condition (1 case).

In 52 of the 54 patients in Group A, the remission induction regimen consisted of daunorubicin (DNR) 60 mg/m<sup>2</sup>/d × 3 days and Ara-C 200 mg/m<sup>2</sup>/d in continuous infusion × 7 days. One patient with AML-M3 received DNR alone for induction (2 mg/kg/d × 5 days). The only patient of Group A older than 60 years of age was treated with mitoxantrone (MTZ) 10 mg/m<sup>2</sup>/d × 3 days and Ara-C (150 mg/m<sup>2</sup>/d in continuous infusion × 7 days). All patients achieving CR were given consolidation chemotherapy with an additional course similar to that of induction. When leukapheresis could not be performed after either induction or consolidation due to the patient's poor clinical condition (nine cases), PBSC were collected after priming with a combination of four drugs (cyclophosphamide 600 mg/m<sup>2</sup> on day 1, vincristine 1.5 mg/m<sup>2</sup> on day 1, Ara-C 200 mg/m<sup>2</sup> every 12 hours s.c on days 1 to 5, and oral prednisone 60 mg/m<sup>2</sup> on days 1 to 5). None of the patients in Group A received hematopoietic growth factors.

In Group B, 43 out of 85 patients received idarubicin (12 mg/m<sup>2</sup>/d × 3 days) and Ara-C (200 mg/m<sup>2</sup>/d in continuous infusion × 7 days) as induction and consolidation therapy. In 39 patients the remission induction regimen was DAV (DNR 45 mg/m<sup>2</sup>/d × 3 days; Ara-C 100 mg/m<sup>2</sup>/12 h × 7 days; VP-16 100 mg/m<sup>2</sup>/d × 5 days). For these patients, consolidation consisted of DNR 45 mg/m<sup>2</sup>/d × 2 days; Ara-C 100 mg/m<sup>2</sup>/12 h × 5 days; VP-16 100 mg/m<sup>2</sup>/d × 5 days. Two patients older than 60 years received MTZ (10 mg/m<sup>2</sup>/d × 3 days) and Ara-C (150 mg/m<sup>2</sup>/d in continuous infusion × 7 days) as induction and consolidation chemotherapy. Finally, one patient received DNR and Ara-C as induction and consolidation with the same chemotherapy regimen depicted for patients in Group A. A further intensification chemotherapy course of Ara-C 1 g/m<sup>2</sup>/12 h × 3 days and MTZ 12 mg/m<sup>2</sup>/d × 3 days was administered to every Group B patient after consolidation. Eight patients in this group received G-CSF (filgrastim, 5 mg/kg/day) after induction and consolidation courses as part of a randomized double-blind

placebo controlled trial in adults with *de novo* AML.<sup>6</sup> The only patient with poor PBSC yields after consolidation underwent an additional leukapheresis procedure in steady-state after intensification. This case was mobilized with G-CSF (filgrastim 10 mg/kg/d × 5 days).

#### *Leukapheresis procedure*

Characteristics of PBSC collection and cryopreservation have been described elsewhere.<sup>4,5</sup> Briefly, leukaphereses were performed during the hematopoietic recovery after chemotherapy, when the WBC count was above 1 × 10<sup>9</sup>/L for two consecutive days. In Group A, daily leukaphereses were performed during 3-5 consecutive days following each course of chemotherapy. In Group B, PBSC collections were performed daily during 2-6 consecutive days only after consolidation. Leukaphereses were performed using a continuous flow blood cell separator (twice the patient's calculated blood volume). An estimate of the number of progenitor cells in each apheresis bag was determined by fluorescence-activated cell-separation analysis of CD34<sup>+</sup> cells (HPCA-2; Becton Dickinson, Mountain View, CA, USA) and 14-day granulocyte-macrophage colony-forming unit (CFU-GM) assay.

#### *Bone marrow collection*

All patients in Group A and 31 out of 35 patients in Group B had bone marrow harvested after consolidation. Bone marrow harvesting was performed according to standard procedures.

#### *Blood stem cell cryopreservation and transfusion*

The marrow and aphereses were not purged and were frozen in a controlled-rate freezer in the vapor phase of liquid nitrogen (Kryo 10; Planner Biomed Products Ltd, Middlesex, United Kingdom). The frozen cells were then transferred to liquid nitrogen and stored at -196°C. Thawing was rapidly performed in a 38°C waterbath without removing the DMSO. The cell suspension was immediately injected into a Hickman catheter placed in a central vein.

#### *Definitions*

Myeloid engraftment was defined as occurring on the first of three consecutive days of absolute neutrophil count (ANC) exceeding 0.5 × 10<sup>9</sup>/L. Graft failure was defined as the lack of myeloid engraftment in patients surviving for at least 28 days after transplantation. Platelet engraftment was defined as occurring on the first of seven consecutive days when the platelet count exceeded 20 × 10<sup>9</sup>/L without transfusional support.

#### *Transplant-related mortality (TRM)*

All deaths of any cause during the first 100 days after transplantation were considered as procedure-related deaths.

#### *Conditioning regimen*

All patients were conditioned with busulfan 4

mg/kg p.o. in divided doses daily for 4 days (total dose 16 mg/kg) and cyclophosphamide 50 mg/kg once daily i.v. on 4 consecutive days (total dose 200 mg/kg). After two days of rest, transplantation was performed on day 0.

#### *Supportive care*

Patients were managed in private, single rooms with positive-pressure filtered air. Mesna was used to prevent hemorrhagic cystitis. Growth factors were not routinely used after myeloablative therapy. A platelet count greater than  $20 \times 10^9/L$  was maintained by platelet transfusions, and packed red blood cells (RBCs) were given when the hemoglobin concentration was lower than 10 g/dL. All blood components were irradiated to 1.5-2.0 Gy and filtered prior to infusion. Every patient received prophylactic antimicrobial agents (ciprofloxacin 500 mg orally every 12 hours, fluconazole 100 mg/d orally, trimethoprim-sulfamethoxazole twice a week and acyclovir 250 mg/m<sup>2</sup> every 8 hours). Patients with neutropenic fever had appropriate cultures and were empirically given broad-spectrum antibiotics; amphotericin B was added when fever lasted more than 5 days.

#### *Statistical analysis*

All data were analyzed as of July 1, 1997. Raw proportions were compared by using the chi-square test. Transplant outcome was analyzed with respect to overall survival (OS), DFS and risk of relapse (RR). OS time was defined as time from transplantation until death from any cause or until last follow-up evaluation for patients who were alive. DFS was calculated from the time of transplantation to the date of death, relapse or last follow-up. Time to relapse was calculated from the time between ABSCT and relapse. The RR was defined as the cumulative probability of relapse, ignoring (i.e., censoring) at death in CR. Survival, DFS, and relapse curves were plotted according to the method of Kaplan and Meier.<sup>7</sup> Statistical comparison between different actuarial curves were based on log-rank tests. Student's t-test was used to analyze differences between two independent means. All calculations were performed by the BMDP program.<sup>8</sup>

## Results

Eighty-nine out of 139 (64%) evaluable patients achieved CR, 36 out of 54 (67%) in Group A and 53 out of 86 (62%) in Group B. Thirty-two were considered as refractory (11 in Group A and 21 in Group B), and there were 19 toxic deaths (14%) (7 in Group A and 12 in Group B).

#### *Feasibility of post-remission treatment*

A search for an HLA-identical sibling donor was performed on each patient below 40 years, and an allogeneic stem cell transplant was proposed to every patient having an HLA-identical sibling. Thus, 18 patients with an HLA-identical sibling donor received an allogeneic stem cell transplant (8 in Group A and

10 in Group B). Two of the 71 remaining patients did not receive consolidation therapy, one due to early relapse, the other to death. Thus, 69 patients received consolidation chemotherapy (27 in Group A and 42 in Group B). After subsequent hematologic recovery, 64 patients continued in CR (25 in Group A and 39 in Group B), and 5 died of toxicity. Finally, all 25 patients in Group A underwent the planned ABSCT. However, in Group B, in which an additional intensification was scheduled, 4 patients did not receive this chemotherapy course (3 relapses and 1 bad clinical condition). The remaining 35 received intensification, and no toxic deaths occurred. Ten of these patients were not finally autografted because of the following reasons: 2 leukemic relapses, 1 patient refusal, 2 protocol violations, 1 insufficient graft cell dose and 4 bad clinical condition.

Fifty patients (25 in Group A and 25 in Group B) did actually receive conditioning regimen with BUCY4 followed by ABSCT. Figure 1 shows the feasibility of the different parts of the protocol in the whole series.

#### *Patient characteristics*

Characteristics at diagnosis of the patient population undergoing ABSCT are given in Table 1. There were no significant differences in the distribution of patients by age, gender, white blood cell count at diagnosis, or FAB subtype between the two treatment groups.

#### *PBSC collection*

The median number of leukaphereses per patient was six (range, 6 to 10) in Group A (3 after induction and 3 after consolidation) and four (range, 2 to 6) in Group B. Median number of mononuclear cells (MNC), CFU-GM and CD34<sup>+</sup> cells administered is shown in Table 2. The total number of CD34<sup>+</sup> cells obtained was higher in Group B (median,  $28.9 \times 10^6/kg$ ) than in Group A (median,  $11.09 \times 10^6/kg$ ). Likewise, median MNC count was higher in Group B ( $12.2 \times 10^8/kg$ ). Finally, there were significantly ( $p < 0.002$ ) more CFU-GM in Group B (median,  $115.06 \times 10^4/kg$ ) than in Group A (median,  $22.15 \times 10^4/kg$ ).

#### *Engraftment*

Forty-six out of 50 patients engrafted. One patient died on day +14, and was not evaluated for engraftment. Three patients had graft failure (two in Group A and one in Group B). The median time to achieve ANC greater than  $0.5 \times 10^9/L$  was 13 days in Group A (range, 8 to 23) and 12 days in Group B (range, 10 to 23). The median time to reach  $1 \times 10^9$  PMN/L was 14 days in Group A (range, 10 to 32) and 13 days in Group B (range, 10 to 61). Twenty-two out of 25 patients in Group A recovered  $20 \times 10^9$  platelets/L in a median of 12 days (range, 9 to 94). The remaining three patients did not achieve a self-sustaining platelet count greater than  $20 \times 10^9/L$  due to graft failure (two cases) or early death (one case). Likewise, in Group B, three patients did not recover  $20 \times 10^9$  platelets/L due

Table 1. Patient characteristics at diagnosis.

Characteristic	Group A	Group B
Total no. of patients	25	25
Sex		
Male	15	13
Female	10	12
Age (years)		
Median	44	40
Range	14-62	18-66
FAB subtype		
M0	1	0
M1	10	6
M2	2	9
M3	1	0
M4	6	5
M5	2	1
M6	2	3
M7	1	1
WBC count (x10 <sup>9</sup> /L)		
Median	42	14
Range	1-186	2-168
Interval diagnosis-ABSCT (months)		
Median	5	6
Range	3-7	5-11

to relapse (two cases) or graft failure (one case). In the remaining patients, median time to reach a platelet count greater than  $20 \times 10^9$  platelets/L was 11 days (range, 6 to 199).

The three patients who failed to engraft received the backup autologous bone marrow on days +25, +41 and +61, respectively. Two of them also received G-CSF or GM-CSF. One patient died before recovery of marrow function, whereas complete hematologic reconstitution occurred in the other two patients. No late engraftment failures have been recorded so far. Although the duration of hospitalization was longer in Group A (median, 23 days; range, 13 to 84) than Group B (median, 17 days; range, 10 to 63), this difference did not reach statistical significance.

#### Regimen-related toxicity

Fever was seen in 43 patients (86%). Infection was microbiologically documented in 19 cases (nine with bacteremia), clinically documented in 19 and possible in 5. No patient had pneumonia. Moderate to severe mucositis was observed in 38 cases (76%) requiring opioid analgesics, total parenteral nutrition or both. Veno-occlusive disease (VOD) occurred in 8 patients (16%), 3 in group A and 5 in group B, and was severe in two. Bladder toxicity was not observed and no cases of busulfan-associated seizures were seen. Transplant-related mortality (TRM) occurred in 4 patients (8%), 3 in Group A (12%) and 1 in Group B (4%). The causes of death were VOD (2 cases), bac-

terial infection (1 case), and intracerebral hemorrhage (1 case). Finally, 1 patient in Group A developed a secondary neoplasia (colon adenocarcinoma) 56 months after transplantation and died five months later while in CR.

#### Outcome

Thirty out of 50 patients relapsed (60%) in a median time of 8 months (range, 1 to 73 months) after ABSCT. Median time to relapse after ABSCT in Group A and B was 7 (range, 1 to 73) and 9 (range, 1 to 48) months, respectively. The majority of relapses (25) occurred within the first year after transplantation. Cumulative RR after transplantation is 67% at 4 years (Figure 2A). The four year probability of relapse for patients of Groups A and B was 64% (95% confidence interval [CI], 60% to 74%) and 81% (95% CI, 67% to 95%), respectively (Figure 2B). Fifteen of the 50 patients (30%) remain alive and disease-free +5 to +74 months after transplantation. DFS for the whole series was 30% at four years (95% CI, 23% to 37%) (Figure 3A). Actuarial DFS was not significantly different for patients in group A (32% at four years, 95% CI, 23% to 41%) and in group B (18% at four years; 95% CI, 4% to 32%) (Figure 3B). Finally, no differences in terms of DFS, RR and OS were seen between those patients in group B who received G-CSF or placebo post-chemotherapy. Twenty-two of the 30 patients who relapsed received a second transplant in untreated relapse with the marrow harvested in CR1 and with the BAVC combination as conditioning regimen. The results of these second transplants in 17 of these patients have been reported elsewhere.<sup>9</sup> Briefly, 13 out

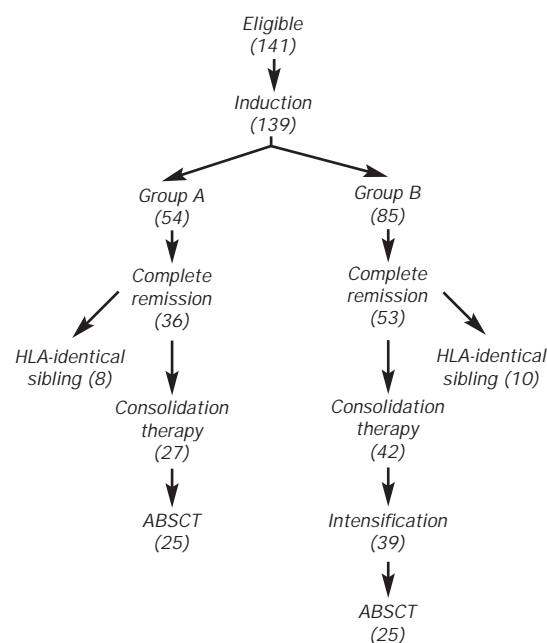


Figure 1. Feasibility of the protocol. The numbers refers to patients at each treatment step. ABSCT denotes autologous blood stem cell transplantation.

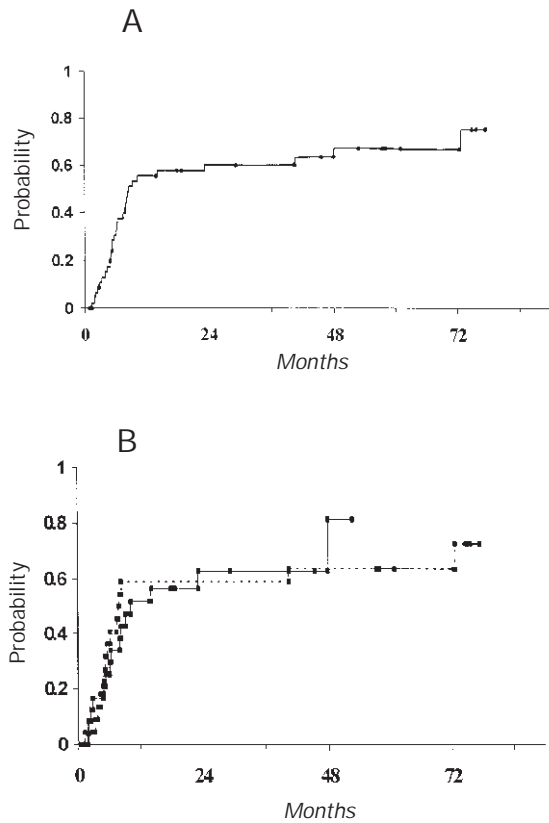


Figure 2. ABSCT in AML patients in first remission. (a) Actuarial risk of relapse of the whole series. (b) Comparison of the actuarial risk of relapse between group A (.....) and group B (—).

of the 17 patients achieved CR (75%). The TRM of the second transplant was 19%, and seven patients were alive and in CR between 7+ and 53+ months, with a DFS probability of 36% at three years. Seven out of the eight patients in relapse after ABSCT who did not proceed to ABMT died of leukemia. The remaining patient is alive and in CR2 five years after an allogeneic BMT. The four-year OS of the 50 patients was 52% (95% CI, 44% to 60%). OS at four years in Group A was 48% (95% CI, 39% to 57%) and 52% (95% CI, 39% to 65%) in Group B.

### Discussion

Several reports have confirmed the feasibility of performing autologous transplantation in AML with PBSC collected after mobilization with either chemotherapy<sup>1-5</sup> or growth factors,<sup>10,11</sup> or both in combination.<sup>12,13</sup> ABSCT is associated with rapid hematopoietic recovery, with a median time to attain  $0.5 \text{ PMN} \times 10^9/\text{L}$  ranging from 10 to 15 days.<sup>1-5,9-11</sup> Likewise, the duration of thrombocytopenia also shortened, with a median time to achieve  $50 \text{ platelets} \times 10^9/\text{L}$  of 19 days.<sup>4</sup> Until recently, high-dose treatments have been limited

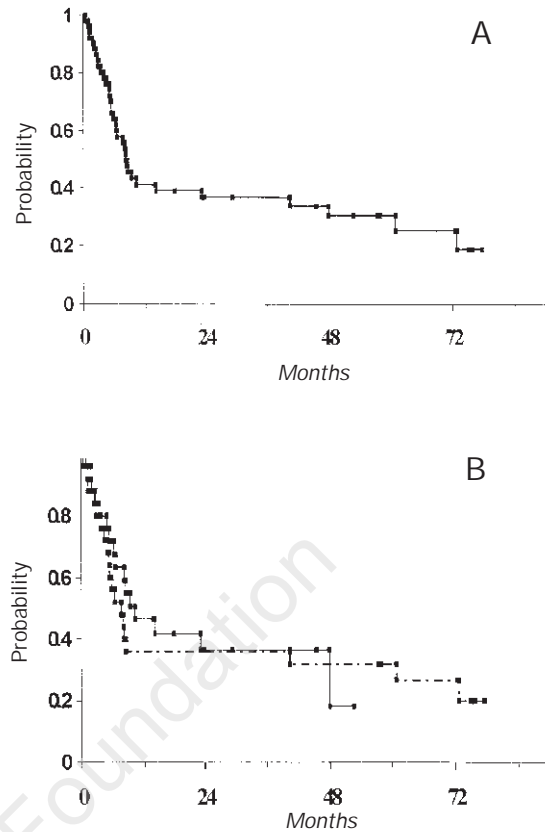


Figure 3. ABSCT in AML patients in first remission. (a) Actuarial disease-free survival of the whole series. (b) According to treatment groups: Group A (.....) and Group B (—).

to younger patients due to the increased risk of treatment-related toxic deaths with age. The fast hematologic reconstitution observed after ABSCT, and the administration of less toxic conditioning regimens could facilitate the administration of high-dose based therapies to older AML patients.<sup>14</sup>

In this study, two different strategies were used including ABSCT as post-remission therapy in adult patients with *de novo* AML: 1) with PBSC collected after induction and after consolidation chemotherapy (Group A) or 2) performing PBSC collection only after consolidation (Group B) and administering an intensification therapy with Ara-C ( $1 \text{ g/m}^2/12 \text{ h} \times 3 \text{ days}$ ) and MTZ ( $12 \text{ mg/m}^2/\text{d} \times 3 \text{ days}$ ) after consolidation (Table 2). The latter approach reduced the number of leukaphereses needed without affecting the final yield of PBSC. The higher number of PBSC collected in Group B could be due to the synergistic effect of chemotherapy and G-CSF administered to some of these patients. Regarding hematopoietic recovery, no significant differences were observed between Groups A and B, although the engraftment kinetics were slightly enhanced in the latter, probably due to the higher

Table 2. Progenitors administered.

	Group A (n=25)	Group B (n= 25)	P value
No. of leukaphereses			
Median	6	4	
Range	6-10	2-6	
MNC x10 <sup>6</sup> /kg			
Mean	6.9	12.2	0.2
Range	3.1-15	2.3-34.7	
CFU-GM x10 <sup>4</sup> /kg			
Mean	22.15	115.06	0.002
Range	1.5-141.6	0-1,228.5	
CD34+ x10 <sup>6</sup> /kg			
Mean	11.09	28.9	0.5
Range	1.5-30.7	1.3-145	

dose of CD34<sup>+</sup> cells infused. Thus, performing leukapheresis only after consolidation allowed us to limit the number of collections, without affecting the PBSC yield or the speed of engraftment.

Some authors have expressed concern about the potential risks of increasing the cytotoxic treatment before autotransplantation in an attempt to prevent recurrence. This strategy could damage the repopulating capacity of the graft slowing down hematopoietic recovery,<sup>15</sup> leading to higher morbidity and TRM. However, despite the greater amount of chemotherapy administered before transplantation in Group B, we did not observe engraftment delay, probably because the higher number of PBSC administered in these patients could partly counteract the greater quantity of chemotherapy. In addition, other series of ABSCT in AML patients have reported no effect on kinetics of engraftment despite the administration of one or two cycles of high-dose Ara-C before transplantation.<sup>11-13</sup>

Although there were no toxic deaths due to intermediate-dose Ara-C, this course of chemotherapy led to selection of patients to be autografted. In fact, all patients in Group A who were in CR after consolidation underwent ABSCT, while in Group B, 10 out of 35 patients in CR after consolidation were not finally autografted. Nevertheless, the similar TRM observed in both groups suggests that the addition of intermediate-dose Ara-C before ABSCT does not critically influence the outcome of ABSCT.

As in ABMT, leukemic relapse remains the most frequent cause of treatment failure after ABSCT. Thus, it is reasonable to develop different strategies addressed at reducing minimal residual disease in the graft as well as in the host. From molecular marker studies,<sup>17</sup> it seems that autologous transplantation carries the risk of reinjecting occult residual leukemic cells. According to some authors, tumor cells in the graft are

the major source of relapse. Optimizing the cell dose infused in PBSC grafts and controlling minimal residual disease by *in vitro* purging could be valid approaches to decreasing the RR in this setting.<sup>17</sup> Some authors have argued that the number of malignant cells in ABSCT would be considerably higher than in ABMT due to the larger cell dose administered with PBSC autografts.<sup>18</sup> However, there are currently no data from autologous transplantation correlating the cell dose infused with the risk of relapse.<sup>19</sup> In the present study, there were no differences in terms of relapse between Group A and Group B patients despite the larger cell dose administered in the latter group, nor did we find any correlation between the number of CD34<sup>+</sup> cells infused and the relapse incidence. On the other hand, based on clinical and preclinical considerations, it has been estimated that conditions in which leukemia will relapse solely from leukemic cells in the graft are rare.<sup>20</sup> This implies that relapse is most often due to inadequate leukemic reduction in the host rather than in the graft. Thus, *in vivo* purging by intensifying chemotherapy before transplantation could theoretically be another way to reduce the number of relapses. In this study, we could not demonstrate that the addition of intermediate dose Ara-C and MTZ after consolidation had a favorable impact on survival, DFS, or RR.

We would be remiss if we did not point out that our results, in terms of DFS and RR, are not satisfactory. Different possible explanations can be considered. Regarding the source of progenitors, although some groups have suggested a higher RR among ABSCT recipients than ABMT recipients in AML,<sup>10,18,21</sup> other series from single institutions<sup>1,3,4,11-13</sup> or registries<sup>2,19,22-24</sup> have suggested similar RR and DFS. In the absence of any existing randomized study comparing patients autografted with PBSC or bone marrow, a definitive answer is not possible. Secondly, our chemotherapy regimen might have been suboptimal, especially the dose of Ara-C administered (6 g/m<sup>2</sup>), and a more intensive or prolonged regimen prior to transplantation might reduce the RR. A recent report by Schiller *et al.* has shown the feasibility of performing ABSCT after high-dose Ara-C (2 g/m<sup>2</sup>/12h × 8 doses) in 43 AML patients in CR1, with an actuarial DFS at 12 months of 47%.<sup>12</sup> Likewise, Martin *et al.*<sup>11</sup> reported the results of ABSCT in 32 patients with AML in first CR. Twenty-two of the patients received 1 or 2 intensification cycles pretransplantation with high-dose Ara-C (1.5 g/m<sup>2</sup>/12h × 6 doses). The authors reported an actuarial probability of relapse and DFS at four years of 42.6% and 57.4%, respectively. In that study, DFS was significantly better in those patients who received intensification therapy before their transplant (68.8% vs 35.5%; p = 0.04).<sup>11</sup> Similar results were published by Reichle *et al.* concerning 16 patients with AML in CR1 who underwent PBSC collections after high-dose Ara-C.<sup>13</sup> In this series, the reported actuarial relapse-free survival at 26 months was 57%. Recently, Gondo *et*

al.<sup>25</sup> reported a five-year DFS of 70.7% in 42 AML patients who underwent ABSCT in CR1 with PBSC collected after intermediate-dose Ara-C. According to these results, it seems reasonable to perform PBSC collections after administration of high-dose Ara-C in an attempt to increase the reduction of the patient's leukemic burden.

As in previous reports on intensive postremission therapy,<sup>26-31</sup> the practical applicability of our protocol was an important issue. In our institution, 56% of the patients achieving CR1 could actually undergo ABSCT, and this figure went up to 70% if we considered only patients lacking an HLA-identical sibling donor. This efficiency ratio of applying autotransplantation is higher than that reported by other single institutions<sup>29</sup> or multicenter trials.<sup>26-28,31</sup> Finally, in other series,<sup>30</sup> the number of patients who relapsed before autotransplantation or who were otherwise excluded because of toxicity, or early mortality was not reported, thus creating a bias toward more favorable-risk patients.

Although some groups have failed to show a prognostic impact of FAB subtype on DFS after ABMT,<sup>26,29</sup> this factor has been proven to act as an adverse prognostic factor in larger series,<sup>28,31</sup> with FAB subtypes other than M2 or M3 having the worse prognosis. Moreover, it is now well known that autologous transplantation is not routinely indicated for FAB-M3 in CR1 due to the excellent outcome with more conservative treatments.<sup>32-37</sup> In our series 24% of the patients were M2 (11 cases, 22%) or M3 (1 case, 2%), whereas in other series these FAB subtypes accounted for between 38% and 44% of the total number of patients.<sup>25,26,28-31</sup> This fact could have played an important role in the better RR and DFS results reported by other groups. On the other hand, it has been recently shown that karyotype at diagnosis is the most important prognostic factor to consider in AML patients grafted (auto or allo) in CR1.<sup>38</sup> Unfortunately, we were not able to study the impact of chromosome abnormalities on the results of ABSCT.<sup>39,40</sup> Marrow cytogenetics at diagnosis were available for only a minority of our patients: six of 25 Group A and 11 of 25 Group B patients (data not shown).

In summary, in our study, the largest including ABSCT for AML in CR1, the majority of patients did complete the treatment protocol. This report also confirms that patients with AML in CR1 receiving ABSCT have rapid engraftment with low TRM. However, autologous transplantation with PBSC was still associated with a high RR. This RR was not reduced either by limiting PBSC collections to only after consolidation or by the administration of intermediate dose Ara-C before transplantation, resulting in an overall DFS no better than that from our historical experience.

#### *Contributions and Acknowledgments*

*JdIR* was involved in study design and wrote the paper. *GFS* was involved in trial design, study coordination and finalization of the paper. *GM* and *JM* contributed to the finalization

of the paper. *JC*, *PS*, *CJ* and *MA* contributed to data collection. *AV*, *IJ* and *AS* contributed to trial design and paper writing. *MAS* was responsible for the final version of the paper and was the senior author.

#### *Disclosures*

*Conflict of interest: none.*

*Redundant publications: no substantial overlapping with previous papers.*

#### *Manuscript processing*

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