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Autologous stem cell transplantation after complete remission and first consolidation in acute myeloid leukemia patients aged 61-70 years: results of the prospective EORTC–GIMEMA AML–13 study

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ABSTRACT

Background and Objectives

The optimal post-remission treatment for elderly patients with acute myeloid leukemia (AML) is presently unknown. Recent studies have reported the feasibility of autologous peripheral blood stem cell transplantation (PBSCT) in this population. We evaluate the outcome of this post-remission approach after complete remission (CR) and consolidation in elderly patients included in the EORTC – GIMEMA AML – 13 trial.

Design and Methods

PBSCT after induction and consolidation chemotherapy was evaluated in patients aged 61 to 70 years old with a WHO performance status 0-1. The induction therapy was mitoxantrone, etoposide and cytarabine (MICE) with or without granulocyte colony-stimulating factor (G-CSF) during and/or after chemotherapy. The consolidation therapy consisted of non-infusional or infusional idarubicin, etoposide and cytarabine (mini-ICE).

Results

Sixty-one patients were scheduled for stem cell harvest by leukapheresis after s.c. recombinant human G-CSF administration initiated after hematopoietic recovery from consolidation. Stem cells were effectively harvested from 54 patients. A median of 2 two aphereses (range, 1–5) were performed, resulting in a median collection of $1.1 \times 10^8$ nucleated cells/kg (range, 2.4–99.8) containing $40.2 \times 10^9$ CFU-GM/kg.

Interpretation and Conclusions

Intensification of remission treatment including autologous PBSCT was feasible in about half of harvested patients aged 61 to 70 years old, and did not improve the general outcome. This shows the limitations of autologous PBSCT and other intensive treatment modalities in elderly AML patients.

Key words: acute myeloid leukemia, elderly, autologous stem cell transplantation.

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The incidence of acute myeloid leukemia (AML) increases with age and more than 50% of AML patients are over 60 years old. These patients have a poor outcome with complete remission (CR) rates of about 50% and less than 20% achieve long-term remission compared with 40% of patients less than 60 years old. Numerous factors may contribute to the inferior outcome with intensive therapy in older patients. Older patients more often have poor-risk leukemic characteristics, such as unfavorable karyotypes, myelodysplastic features, or a chemoresistant profile. Furthermore, older patients often have more or more severe comorbid conditions than younger patients and tolerate prolonged pancytopenia and intensive therapy less well.

The addition of etoposide to an anthracycline/cytarabine regimen during induction and consolidation has been shown to prolong CR in young adults with newly diagnosed AML. There is general agreement that some sort of post-remission treatment should be used after reaching CR. Its intensity, however, is an open question particularly in the elderly. Several trials have suggested that consolidation of AML in first complete CR with high-dose cytarabine is not usually feasible and associated with more toxic deaths and relapses in patients over 60 years old when compared with younger patients. A myeloablative regimen followed by autologous stem cell transplantation reduces the relapse rate in young adult AML patients. Furthermore, peripheral blood stem cell support has been shown to be superior to bone marrow support in terms of hematologic recovery, with less than 10% transplant-related mortality. Several recent studies have reported the feasibility of autologous peripheral blood stem cell transplantation (PBSCT) in elderly AML patients, including patients aged above 70 years. These observations allowed us to propose administering one or more intensive consolidation therapy regimens to a larger number of patients at increasing ages.

We, therefore, studied the outcome of combining these approaches in elderly patients with newly diagnosed AML. The conditioning schedule for these elderly patients needed to be myeloablative without excessive toxicity. We selected the BAVC conditioning schedule which is remarkably well tolerated in old patients. The aim of the present study was to confirm the feasibility of peripheral blood stem cell collection and the tolerance of the BAVC conditioning regimen and to evaluate the outcome of peripheral blood stem cell support after one or two induction chemotherapy course and one standard dose consolidation course in AML patients ≤70 years of age, registered in the EORTC-LG/GIMEMA trial (AML-13).

**Design and Methods**

**Study design**

The AML-13 trial was a randomized phase III study carried out by the European Organization for Research and Treatment of Cancer and Gruppo Italiano Malattie Ematologiche dell’Adulto (EORTC/GIMEMA) leukemia groups in 53 European centers. This prospective trial was designed (Figure 1) for patients 61–80 years of age with previously untreated de novo or secondary AML. The final protocol was approved by the EORTC Protocol Review Committee and by the Ethical Committee of each participating center. Before inclusion all patients had to sign informed consent which was in accordance with the Helsinki protocol.

The two first objectives of the study were: (i) to determine the efficacy and toxicity of adding granulocyte colony-stimulating factor (G-CSF) to induction chemotherapy; (ii) to assess the role of non-infusional mini-ICE as consolidation relative to i.v. mini-ICE. Detailed analyses of the induction therapy and consolidation chemotherapy have been reported elsewhere.

We report here the results of the last (optional) objective of this trial, namely the feasibility of myeloablative chemotherapy followed by autologous PBSCT as a second consolidation course. At selected centers, complete responders with a good performance status and an age ≤70 years were offered an intensified second consolidation consisting of myeloablative chemotherapy followed by re-infusion of autologous peripheral blood stem cells collected after hematologic recovery following the first consolidation course.

**Eligibility criteria**

Patients aged more than 60 years and ≤80 years old, with newly diagnosed de novo AML or AML secondary to a preceding myelodysplastic syndrome (MDS) or to toxic exposure were eligible for this trial, provided they had a good performance status (grade 0, 1 or 2, WHO scale) and no severe organ failure. Patients were eligible for the high dose chemotherapy with peripheral blood stem cell support as the second consolidation course if they met the following criteria after the first consolidation course: persistence of CR, absence of organ damage, the absence of severe infection, WHO performance status 0 or 1, age 61-70 years old at registration.

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**Figure 1.** Design of AML-13 study.
Criteria of evaluation

AML was diagnosed according to the French-American-British (FAB) criteria\textsuperscript{27–29} and a central review was done in all cases. Bone marrow was assessed for response approximately 3 weeks after the end of chemotherapy. The Cancer and Leukemia Group B (CALGB) criteria were used to determine response to treatment and relapse.\textsuperscript{29} The International System for Cytogenetic Nomenclature (ISCN) was used for the cytogenetic classification.\textsuperscript{30} The cytogenetic data were reviewed centrally. Twenty analyzed metaphases were required to include a patient in the group with a cytogenetically normal karyotype (NN group). Complex abnormalities were defined as a clone with at least four unrelated abnormalities. The patients with unknown, not done, or unsuccessful cytogenetics were grouped together as unknown. Abnormalities 16q(22) and t(8;21) were considered favorable risk abnormalities, whether other abnormalities were present or not. NN karyotypes or those with −Y only were classified as intermediate risk. Entire or partial deletions of chromosome 5 and/or 7, the presence of complex abnormalities (more than three abnormalities) or trisomy 8 were considered unfavorable prognosis. Patients with other abnormalities were pooled into a separate cytogenetic risk group (other).

Chemotherapy

The design of the trial is shown in Figure 1. Induction chemotherapy included one or two courses of MICE combining mitoxantrone 7 mg/m\textsuperscript{2} day i.v. on days 1, 3, and 5, with etoposide 100 mg/m\textsuperscript{2} day i.v. on days 1 to 3 and cytarabine 100 mg/m\textsuperscript{2} day i.v. as a continuous infusion, on days 1 to 7. Recombinant human G-CSF (rHuG-CSF) (lenograstim, 150 µg/m\textsuperscript{2} day) was randomized to be given during and/or after chemotherapy. In arm 1A, patients did not receive any rHuG-CSF, while patients received it on days 1 through 7 in arm 1B, on days 8 through 28 in arm 1C, and on days 1 through 28 in arm 1D. Patients in CR after one or two courses of induction treatment were to receive two courses of consolidation, administered as early as possible following hematologic recovery. Consolidation was randomized between i.v. mini-ICE vs non-infusional mini-ICE. Intravenous mini-ICE comprised idarubicin 8 mg/m\textsuperscript{2} day i.v. on days 1, 3, and 5, associated with etoposide 100 mg/m\textsuperscript{2} day on days 1 to 3 and cytarabine 100 mg/m\textsuperscript{2} day i.v. as a continuous infusion, on days 1 to 5. Non-infusional mini-ICE consisted of idarubicin 20 mg/m\textsuperscript{2} day p.o. on days 1, 3, and 5, associated with etoposide 100 mg/m\textsuperscript{2} day p.o., twice daily, on days 1 to 3 and cytarabine 50 mg/m\textsuperscript{2} day s.c., twice daily, on days 1 to 5.

Stem cell transplantation

After receiving the first consolidation treatment, patients (at 18 participating centers) aged less than 70 years with a performance status <2 were scheduled for peripheral blood stem cell harvest. The harvest was performed by apheresis, beginning after 3 to 5 days of subcutaneous treatment with G-CSF (lenograstim) at a daily dose of 150 µg/m\textsuperscript{2}, initiated within 2 weeks after hematologic recovery from the first consolidation course. According to the protocol, the total blood stem cell harvest should contain a target dose of at least $2 \times 10^6$ CD34\textsuperscript{+} cells/kg. As a surrogate marker for the mobilizing capacity after consolidation treatment, we adopted the highest yield of a single apheresis cycle. The total number of CD34\textsuperscript{+} cells harvested could not be used for this purpose since this was influenced by the predefined target of $2 \times 10^6$ CD34\textsuperscript{+} cells/kg. PBSCT was performed after a BAVC conditioning regimen consisting of carmustine (BCNU) 800 mg/m\textsuperscript{2} on day –6, amsacrine 150 mg/m\textsuperscript{2} day on days –5, –4, and –3, etoposide 150 mg/m\textsuperscript{2} day on days –5, –4, and –3, and cytarabine 300 mg/m\textsuperscript{2} day on days –5, –4, and –3.

Supportive care

Supportive care during induction, consolidation and autologous transplantation included the use of reverse isolation or sterile room, prophylactic red blood cell and platelet transfusions, antibacterial and antifungal gastrointestinal decontamination, and the empirical use of antibiotics if the patient became febrile.

Statistical analysis

Disease-free survival (DFS) was defined from the date of CR to the date of relapse or death, or last contact with patient in continuous CR. The time to relapse and time to death in CR were calculated as the DFS, but the follow-up of patients who died in CR and those who relapsed were censored at that moment for these two analyses. By definition, all patients who died in CR were considered to have died from a treatment-related cause. Overall survival (OS) was defined as the time from CR to death or last contact with the patient. DFS and OS probabilities were calculated using the Kaplan and Meier product-limit estimate method. The standard errors of the estimates were calculated according to Greenwood’s method. The estimates of the incidence of relapse and of death in CR, and their corresponding standard errors, were obtained using the cumulative incidence method, in which the risks of death in CR and of relapse were considered as competing risks.\textsuperscript{31} Duration of recovery was defined as the time from the start of stem cell transplantation until granulocyte or platelet recovery; the follow-ups of patients without recovery were censored at day 120. The database was frozen on November 2003.
All computations were made using SAS 8.2 statistical software (SAS Institute Inc., Cary, NC, USA).

## Results

### Feasibility of autologous SCT

From December 1995 to February 2001, a total of 757 patients (median age, 67 years; range, 61–80 years) were registered in the AML-13 trial. Before starting the trial, centers were asked to choose between the use of a second mini-ICE consolidation course in all patients aged 61 to 70 years in good clinical condition (WHO performance status 0 or 1), or to administer myeloablative chemotherapy followed by autologous PBSCT. Eighteen participating centers that chose the second therapeutic option entered 445 AML patients, of whom 278 were aged less than 71 years. One hundred and fifty-nine of these patients (57%) achieved a CR, of whom 134 were randomized to the consolidation arm (non-infusional or i.v. mini-ICE), and effectively received the assigned consolidation course. Patients with a WHO performance status 0 or 1 were theoretically scheduled for stem cell harvest by leukapheresis after 3-5 days of subcutaneous recombinant human G-CSF initiated after hematopoietic recovery from consolidation. Out of 152 patients who were still in CR after the first consolidation course, 113 had a performance status <2. Among those, 59 (47%) patients were scheduled for stem cell harvest, whereas 54 were not. Reasons for not planning stem cell harvest were early relapse (15 patients), toxicity of the first consolidation course (20 patients), patients’ refusal (6 patients), or miscellaneous (13 patients). Stem cells were effectively harvested from 52 patients, of whom 38 had an adequate harvest. Among these, five patients have not been transplanted due to an early relapse (3 patients) or refusal of further treatment (2 patients). Autologous PBSCT was performed in 33 patients following conditioning with the BAVC regimen (Figure 2). Two patients with a performance status of 2 also underwent stem cell harvesting and received autologous PBSCT at their physicians’ decision. These two patients were included in the following calculations.

### Peripheral blood stem cell collection

Overall 61 patients (median age, 65 years; range, 61-70 years) were scheduled for stem cell harvest. Their initial cytogenetics, FAB subtypes and main treatment characteristics are shown in Table 1. Thirty-three patients received i.v. mini-ICE as the first consolidation course, while 28 received non-infusional mini-ICE. The median duration of lenograstim administration was 5 days (range, 2 – 27 days). Stem cell harvest was performed in a stable phase in all patients, except in one case in whom G-CSF was started on day 6 of the consolidation
Figure 3. Disease-free survival from complete remission achievement in patients scheduled for autologous stem cell transplantation (SCT) (61 patients). N: number of patients; O: observed number of events (relapse or death without relapse).

Figure 4. Disease-free survival from complete remission achievement in patients from the 18 participating centers, aged less than 70 years, with a performance status <2 at the evaluation of the first consolidation, according to treatment received: autologous stem cell transplantation (33 patients) or a second consolidation chemotherapy (49 patients). N: number of patients; O: observed number of events (relapse or death without relapse).

course and harvest performed at the time of cell recovery. In seven of these 61 patients, the number of CD34+ circulating cells remained below the threshold for starting an apheresis in spite of administration of recombinant human G-CSF administration. The median time between the start of the first consolidation course and the start of lenograstim was 45 days (range, 6–124 days). In the 54 patients in whom a harvest was performed, a median of two aphereses (range, 1–5) were performed, resulting in a median collection of 11.7×10^6 nucleated cells/kg (range, 2.4–99.8) containing 40.2×10^6 CFU-GM/kg (range, 0–768.8), and 5×10^6 CD34+ cells/kg (range, 0.1–99.8). Based on the highest harvest of CD34+ cells obtained during a single apheresis, 12 patients were considered to have a low CD34+ yield (<1×10^6/kg), 27 patients an intermediate CD34+ yield (1–6.9×10^6/kg), and 15 patients a high CD34+ yield ≥7×10^6/kg. The cumulative CD34+ yield was considered to be adequate for PBSCT in 40 patients. The median follow-up from the start of the first consolidation course was 4.6 years. For the whole group of 61 patients, the median DFS was 1.0 years and the 3-year DFS rate was 21% (95% CI: 11–31%) (Figure 3), while the median OS was 1.5 years and the 3-year OS rate was 32% (95% CI: 20–44%). The 3-year incidence of death in CR was 10% (SE=4%).

A total of 26 patients could not be autografted due to inadequate/no harvest (21 patients), early relapse (3 patients), or treatment refusal (2 patients). Among them, 10 patients received a second course of consolidation. At the time of analysis, three of the 26 patients not autografted were still in continuous CR, 22 patients had relapsed and 1 had died from toxicity while in CR. By intent-to-treat analysis, the treatment outcome of patients who had been scheduled for peripheral blood stem cell harvesting in the two arms of second randomization (i.v. mini ICE vs non-infusional mini ICE) was similar. The highest CD34+ yield, considering the cut-points at 1 and 7×10^6/kg, as well as the total yield of CD34+ harvested, taking the cut-points at 2 and 10×10^6/kg, did not appear to be predictive for the DFS from the start of first consolidation.

The BAVC conditioning regimen and peripheral blood stem cell support

Autologous PBSCT was performed in 35 patients following the BAVC regimen. The median time from achieving CR to time of transplant was 3.2 months (range, 1.9–6.8 months). The median age of transplant- ed patients was 64 years (range, 61–69 years). Patients were grafted with a median of 10.3×10^6 nucleated cells/kg (range, 0.9–20.9) containing a median of 38.3×10^6 CFU-GM/kg (range, 0–768.8) and 5×10^6 CD34+ cells/kg (range, 1.9–38.8). In one patient, the total blood stem cell harvest remained below the target dose of 2×10^6/kg body weight CD34+ cells but by decision of the physician this patient underwent PBSCT. All patients had successful engraftment. The median time to platelet recovery >20×10^9/L was 23 days (range, 14–120+ days) and that of platelet recovery >150×10^9/L was 120 days (range, 21–370 days) following transplantation. The median time to granulocyte recovery >0.5×10^9/L was 24 days (range, 15–120+ days) and that of granulocyte recovery >1.5×10^9/L was 41 days (range, 17–120+ days) following transplantation. Severe non-hematologic toxicities (WHO grade ≥3) included sepsis (4 patients), pulmonary infection (2 patients), skin toxicity (2 patients), mucositis (1 patient), diarrhea (1 patient), nausea (1 patient), cardiac dysrhythmia (1 patient), and hypotension (1 patient).

At the time of analysis, the median follow-up from
transplantation was 5.0 years. Eight autografted patients were still in continuous CR, 22 patients had relapsed (at a median of 7 months, range: 1.7–50.6 months) and five had died while in CR (at a median of 3.4 months, range: 2.4–24.5 months). For the 35 autografted patients, the estimated median DFS and OS from transplantation were 1.1 and 1.6 years, respectively. The 3-year DFS rate was 28% (95% CI: 13–43%) (Figure 4) and the 3-year OS rate was 39% (95% CI: 22–52%). The 3-year relapse incidence was 57% (SE=9%), while the 3-year incidence of death in CR was 15% (SE=6%). Five patients died while in CR, two from severe infection, two from cardiovascular dysrhythmias and one from an unknown cause. There were no obvious differences in DFS among patients from the 18 participating centers receiving autologous stem cell transplant and those receiving a second course of consolidation chemotherapy (Figure 4).

Discussion

Preliminary reports have suggested that autologous stem cell transplantation is feasible in elderly patients with AML. However those reports were either from a retrospective study or involved only a small number of patients and did not give accurate information about the potential application of the procedure in this patient population, or used different conditioning regimens or mixed patients with different stages of disease. We, therefore, addressed the question of autologous SCT in a large, prospective, multicenter trial.

Older patients with AML are obviously more prone than younger patients to develop complications related to treatment. Morbidity associated with standard dose busulfan/melphalan or cyclophosphamide/total body irradiation bone marrow ablative conditioning regimens resulted in inappropriate complications for elderly patients. A pilot study has reported the follow-up of 19 elderly patients submitted to autologous stem cell transplantation after idarubicin or mitoxantrone/etoposide/cytarabine induction and consolidation courses. Conditioning regimens varied and included BCNU 500 mg/m² in six patients, busulfan 16 mg/kg in nine patients, and BAVC in four patients. Based on this experience, BAVC was chosen as the conditioning regimen in our study. This choice was due to the limited extra-hematologic toxicity apart from a relevant incidence of mucositis and severe infections during the aplastic phase. No other extra-hematologic toxicities were documented and no significant impairment of cardiac and respiratory function was observed after autologous stem cell transplantation. Furthermore, hospital stay and the kinetics of engraftment seem to be comparable to those reported in younger patients.

We confirmed these findings in the present study, in which only patients aged 61-70 years old, with a good performance status after first consolidation, were included. Sixty-one patients were considered eligible for stem cell harvest and 57% of them mobilized a number of CD34+ cells sufficient to perform an autotransplant. This indicates a major selection, the transplant approach reaching only a minority of patients. Resistant disease, toxicity and logistic problems reduced the number of patients to whom the transplant procedure could actually be applied. These results confirmed the inconstant application of this post-remission strategy in elderly patients and emphasized the overevaluation of feasibility in previous published small series. Toxicity after transplantation was comparable to that observed in the pilot study in which two patients (10%) died, and grade 2 – 4 WHO extra-hematologic toxicity was observed in 40% of cases. In our study all patients had successful engraftment. However, the median platelet recovery to >20×10⁹/L took 120 days despite a sufficient number of CD34+ cells having been infused. The number of reinfused CD34+ cells and age at the time of transplantation has been shown to be major factors influencing platelet engraftment. On an intent-to-treat analysis, the two randomization arms, non-infusional mini ICE and i.v. mini-ICE, provided comparable DFS and OS. The treatment outcome of the 61 patients who had been scheduled for peripheral blood stem cell harvesting in the two randomization arms was also similar. The 3-year relapse incidence was high (69%) and median DFS from CR was 1.12 years.

CD34+ peripheral blood cells reinfused after a myeloablative regimen did lead to full bone marrow reconstitution. There is still no agreement regarding the

<p>| Table 2. Results of patients who underwent autologous stem cell transplantation (n=35). |</p>
<table>
<thead>
<tr>
<th>Features</th>
<th>Results</th>
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<tr>
<td>Stem cell harvest</td>
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<tr>
<td>Nucleated cells/kg</td>
<td>10.3 (0.9–20.9)*</td>
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<tr>
<td>CFU-GM/kg</td>
<td>38.3 (0–768.8)*</td>
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<tr>
<td>CD34+ cells/kg</td>
<td>5.9 (1.9–38.8)*</td>
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<td>Hematologic toxicity</td>
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<td>Platelet recovery to 20×10⁹/L</td>
<td>23 days (14–120)+</td>
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<td>Platelet recovery to 150×10⁹/L</td>
<td>120 days (21–370)+</td>
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<td>Granulocyte recovery to 0.5×10⁹/L</td>
<td>24 days (15–120)+</td>
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<tr>
<td>Granulocyte recovery to 1.5×10⁹/L</td>
<td>41 days (17–120)+</td>
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<td>Outcome</td>
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<td>DFS from transplantation</td>
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<td>Median</td>
<td>1.1 years</td>
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<td>3-year rate</td>
<td>28%</td>
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<td>OS from transplantation</td>
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<td>Median</td>
<td>1.6 years</td>
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<td>3-year rate</td>
<td>39%</td>
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*median (range); DFS: disease-free survival; OS: overall survival.
Although it is generally assumed that CD34 peripheral blood stem cells is not five (14%), although harvested peripheral blood stem cells might be cells/kg is optimal, and did not show contamination than does bone marrow. In a previous retrospective study, a higher relapse incidence was demonstrated in patients receiving a stem cell transplant from peripheral blood stem cells as compared to those receiving stem cell transplant from bone marrow stem cells (63% vs 44%). Although it is generally assumed that reinfusion of more than 5x10^6 CD34^+ cells/kg is optimal, the number of CD34^+ peripheral blood stem cells is not necessarily an accurate indicator of an adequate harvest in AML patients. Grafts involving a high number of CD34^+ harvested peripheral blood stem cells might be contaminated by more clonogenic malignant cells responsible for a high relapse rate.

The prevalence of co-morbid conditions increases with age. Intensity of therapy is likely to exacerbate or trigger clinical problems that may contribute to morbidity and mortality during the transplantation process. Although, recent data from patients with hematologic malignancies suggest that a very low transplant-related mortality can be achieved in elderly patients using mobilized peripheral blood stem cells and conditioning regimens without total body irradiation, five (14%) transplant-related deaths were recorded in our series. Actually, the impact on treatment outcome seen in patients with increased comorbidity has recently been shown to be independent of the functional status. While not specific to elderly AML patients, morbidity scales, as recently suggested, may be useful to identify the impact of comorbidities on treatment decisions.

In the absence of new drugs or efficient modulation of resistance, treatment of AML is based on the optimization of delivery of currently active drugs. Our report confirms that BAVC followed by peripheral blood stem cell support can be safely incorporated in the therapeutic strategy for AML patients over 60 years of age. However, post-induction therapy including autologous stem cell transplantation is only feasible in about half of patients aged 61 to 70 years old in whom harvesting is performed. Overall, our study demonstrates that autologous stem cell transplantation has a very minor role, if any, as a postconsolidation approach in older patients with AML. In our study, the long-term survival rate after autologous stem cell transplantation was similar to those reported in retrospective studies. Although generating multiple biases, the comparison of patients undergoing autologous stem cell transplantation with those receiving the second consolidation course did not confirm results of previous series and did not show any real benefit in favor of the transplant approach in terms of DFS. Furthermore, the outcomes described above overestimate the true situation. The trial enrolled patients with relatively favorable prognoses, and eligibility criteria precluded the entry of patients who were not ambulatory or who had abnormal hepatic, renal, or cardiac function. One conclusion is that there are limitations and little evidence that treatment by autologous stem cell transplantation or other intensive treatment modalities is improving the ultimate outcome of disease in the elderly. Meanwhile, several new agents are emerging that require testing, alone or in combination.

**Conflict of Interest**

The authors reported no potential conflicts of interest.

**Authors' Contributions**

All authors participated in the design of the study. XT: drafted the manuscript and recruited patients; SS: performed the statistical analyses and reviewed the manuscript; BR, GL, GB, GF, WF, MV and TdW: recruited patients; SA and UJ: conducted the study, recruited patients, reviewed the manuscript and gave final approval.

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