BAVC Regimen and Autologous Bone Marrow Transplantation in Patients With Acute Myelogenous Leukemia in Second Remission

By Giovanna Meloni, Paolo De Fabritiis, Maria Concetta Petti, and Franco Mandelli

Twenty-one acute myelogenous leukemia (AML) patients were submitted in second remission (II CR) to BAVC conditioning regimen followed by unpurged ABMT. Transplant was done after a median of 2 months from II CR (range, 1 to 13). Median first remission (I CR) duration was 16 months (range, 1-35). Conditioning regimen was well tolerated, with no major extra-medullary toxicity. One patient died during aplasia from fungal sepsis. Of the 20 evaluable patients, nine relapsed after a median time of 6 months (range, 2 to 18). Eleven patients are in continuous complete remission (CCR) after a median follow-up of 40 months (range, 24 to 63). The duration of II CR has exceeded the duration of I CR in all patients in CCR. Projected probability of disease-free survival is 52% at 63 months.

PATIENTS WITH ACUTE myelogenous leukemia (AML) in first remission (I CR) have a 15% to 25% probability of cure. Better results are reported in children, 30% to 40% of whom are probably cured.1 After relapse, prognosis in both children and adults is very poor. Although it is possible to achieve a second remission (II CR) with intensive polychemotherapeutic schedule, in more than 50% of the cases, a probability of long-term survival (LTS) of less than 5% has been reported in the majority of studies. 2

New regimens of intensive polychemotherapy as post-remission treatment have been used in I CR. The results, although preliminary, demonstrate the feasibility of these new strategies, with a significant increase in the proportion of LTS.3 When patients in II CR are considered, no data concerning similar intensive post-remission schedules are available so far.

Higher doses of chemo/radiotherapy followed by autologous stem cell reinfeusion represent a promising therapeutic approach in the treatment of acute leukemia patients. Autologous bone marrow transplantation (ABMT) was primarily evaluated in patients with acute leukemia in relapse.4 In this area many groups established that new remissions could be achieved in 70% to 80% of cases, but these were of short duration with less than 5% being long-term survivors.5 These results have led to anticipation of ABMT at early stages of the disease, during CR. In I CR transplanted patients, a 40% to 50% probability of LTS has been reported. However, results from different centers are not easily comparable because of heterogeneity of population and methods (eg, induction treatment, conditioning regimens, consolidation of remission, timing of transplant, type of disease, purging procedures).6 ABMT represents an elective treatment in AML in II CR, since the 20% to 30% chance of LTS achieved in transplanted patients is clearly superior as compared with the results of chemotherapy alone.7

We report 21 patients affected by AML in II CR treated with BAVC high-dose chemotherapy regimen followed by cryopreserved autologous bone marrow reinfeusion. The toxicity and the therapeutic efficacy of this approach will be analyzed.

PATIENTS AND METHODS

Between October 1984 and August 1988, 21 consecutive AML patients without HLA compatible donor and suitable for a regimen of aggressive chemotherapy entered this study. In all cases, an informed consent was obtained. The results were analyzed as of January 31, 1990. Details of patients’ characteristics are shown in Table 1: median age was 24 years (range, 1 to 47); eight were female; and according to FAB classification, the patients were allocated as M, (6), M, (6), M, (4), M, (4), M, (1). Median first CR duration was 16 months (range, 1 to 35). ABMT was done after a median of 2 months (range, 1 to 13) from reaching second CR. Seven patients were induced in II CR with high-dose cytosis arabinoside (ARA-C; 3 g/m² twice a day x 3 days) plus either AMSA or Idarubicin or L-asparaginase; 10 patients with intermediate dose of ARA-C (1 g/m²/d x 6 days) plus Mitoxantrone (6 mg/m²/d x 6 days). Four patients received ARA-C at conventional doses plus either daunorubicin (3 + 7 schedule) in one patient or AMSA and 6-thioguanine (AAT schedule) in the other three cases. After complete remission, a consolidation with the same drugs used for induction was done in 12 cases while the others underwent directly ABMT.

Bone marrow processing. The techniques of marrow collection, cryopreservation, and reinfeusion have been previously described.7 Seventeen patients underwent marrow collection immediately before the start of pretransplant chemotherapy, and four were harvested during I CR. A median of 1.4 x 10⁸ nucleated marrow cells per kilogram of body weight (range, 2 to 3.0) were collected from posterior iliac crests while patients were under general anesthesia.

Preparative regimen. All patients received prior bone marrow reinfeusion, a four-drug original schedule (BAVC; consisting of BCNU [800 mg/m² on day -6]. AMSA [150 mg/m² on days -5, -4, and -3], VP-16 [150 mg/m² on days -5, -4, and -3], and ARA-C [300 mg/m² continuous infusion on days -5, -4, and -3]) followed after 2 days rest by bone marrow infusion.

Supportive care. Patients were nursed in a reverse isolation single room, with a central venous catheter placed for the administration of chemotherapy, blood products, and fluids. Bowel decontamination was done with either norfloxacine or cotrimoxazole. Broad spectrum antibiotics were given for fever during aplasia, adding amphotericin B when a persistent fever or a documented fungal infection occurred. All patients at risk for the recurrence of herpes virus infection received prophylactic intravenous acyclovir.
All blood products were irradiated with 20 Gy before infusion to prevent possible graft-versus-host reactions.

**RESULTS**

_Toxicity._ Conditioning regimen was well-tolerated and only various degrees of nausea and vomiting were observed during administration of chemotherapy. Four patients developed severe oral mucositis that generally resolved at the time of bone marrow engraftment. No episodes of severe hemorrhage were observed. Sixteen patients had fever during aplasia: in 10 of 16 (62%), fever was associated with positive cultures for bacteria (nine patients) or fungus (one patient). One patient died in aplasia 1 month after bone marrow reinfusion of candida albicans sepsis. In 2 of 21 patients, clinical symptoms of pulmonary distress, including rapidly progressing dyspnea, dry cough, and tachypnea were observed at 3 months from transplant. Pulmonary function tests revealed arterial hypoxemia, marked reduction of residual volume and total lung capacity, and decreased CO₂ diffusion; a pattern of diffuse interstitial infiltration was observed at chest x-ray of the two patients. Bacterial, viral, and fungal etiologies were excluded by culture and serologic tests; bronchoalveolar lavages were not done. Low-dose steroid treatment was given, resulting in disappearance of all clinical signs and x-ray normalization in both cases. Periodic lung-function studies showed progressive improvement of restrictive pattern with return to pretransplant values after 6 and 8 months, respectively.

_Engraftment._ One patient died on day +31 without evidence of engraftment. In the remaining 20 patients, the median time required to attain an absolute neutrophil count in excess of 0.5 × 10⁹/L was 18 days (range, 11 to 35). A platelet count exceeding 50 × 10⁹/L was observed after a median of 31 days (range, 13 to 180). Only six cases took more than 50 days to achieve 50 × 10⁹/L platelets. No correlation was observed between the number of nucleated bone marrow cells or granulocyte-macrophage colony-forming cells reinfused and the rate of hematologic recovery.

**Follow-up.** As of January 31, 1990, 11 of 20 evaluable patients are in continuous complete remission (CCR) with a median follow-up of 40 months (range, 24 to 63). Eight patients relapsed in the bone marrow, and one patient had an isolated meningeal relapse. Median time to relapse was 6 months (range, 2 to 18). In all CCR patients the duration of CR was shorter compared with both overall CR and post-ABMT CR duration. Among patients relapsed after ABMT, a II CR duration greater than the first one was observed only in the case that had an isolated central nervous system (CNS) relapse.

Projected probability of disease-free survival (DFS) of all 21 transplanted patients at 63 months is 52% (Fig 1), with a probability of relapse of 45% (Fig 2). Of the four patients who received ABMT with marrow collected and cryopreserved in I CR, three relapsed after 4, 6, and 6 months, respectively; and one is in CCR after 50 months. Among the remaining 17 patients who underwent ABMT with marrow collected in II CR, 10 are still in CCR with a DFS of 59% at 63 months (Fig 1). No relationship between probability of CCR and length of first CR, FAB classification, time of bone marrow collection, sex, age, and consolidation therapy was observed. According to second induction treatment, a trend...
DISCUSSION

In this study, 21 AML patients in II CR were submitted to BAVC regimen followed by autograft. Eleven patients (52%) are in CCR after a median follow-up of 40 months (range, 24 to 63).

The possibility of achieving long-term DFS (more than 40% at 60 months) in patients transplanted in II or III CR was first reported by the Baltimore group that utilized marrow pre-incubated with 4-HC and the original busulphan and cyclophosphamide polychemotherapeutic schedule. The 1989 European Bone Marrow Transplantation Group (EBMTG) survey on 136 patients with II CR AML autografted with marrow, purged or not, reports a DFS of 32% at 40 months. Our results seem promising considering that unselected and consecutive patients were transplanted without purging procedures. Furthermore as opposed to other conditioning regimens, no major problems were associated with BAVC. Only one patient died of fungal sepsis, and no late life-threatening side effects were observed during follow-up of transplanted patients. Otherwise our experience with BAVC in 55 AML patients autografted in I CR confirms the feasibility of this schedule, with less than 5% of transplant procedure-related deaths. Apart from data by the Leukemia Intergroup, which reported more than 30% of DFS at 12 months in first relapse AML patients induced into a second remission with high dose ARA-C + AMSA, once patients relapse, few, if any, can be cured by further chemotherapy without bone marrow transplantation. Therefore, ABMT represents to date a promising alternative approach to allogeneic bone marrow transplantation. However, no conclusions can be drawn from our study and other experiences about its exact role, because of the small series of patients and the heterogeneity of populations in the retrospective studies.

There is still a variety of major issues to be solved. First, what is the best conditioning regimen in terms of feasibility and antileukemic effect? Second, can chemotherapy schedule in relapse influence the outcome of patients? Third, does the addition of purging procedures to an autologous transplant increase relapse free survival? Prospective cooperative randomized trials are required to answer these questions.
### APPENDIX

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<tr>
<th>Abbreviation</th>
<th>Type of Initial Chemotherapy</th>
<th>Day</th>
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<tr>
<td>3 + 7</td>
<td>Daunorubicine</td>
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<tr>
<td></td>
<td>Cytosine arabinoside</td>
<td>1-7</td>
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<tr>
<td>2 + 5</td>
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<td>DAT</td>
<td>Daunorubicine</td>
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<td></td>
<td>6-Thioguanine</td>
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<td>Cytosine arabinoside</td>
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<td>6-Thioguanine</td>
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<td></td>
<td>Etoposide</td>
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<td></td>
<td>Daunorubicine</td>
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<td>Asnasi</td>
<td>Asparaginase</td>
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<tr>
<td>Intensive consolidation</td>
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<td></td>
<td>AMSA</td>
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<td></td>
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<td></td>
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<tr>
<td>Intensive post-consolidation</td>
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<td></td>
<td>Daunorubicine</td>
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Abbreviations: CI, continuous infusion; PO, orally; SC, subcutaneously.

### REFERENCES


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