

AUTOLOGOUS STEM CELL TRANSPLANTATION IN ELDERLY AML PATIENTS

A randomised comparison of idarubicin vs mitoxantrone, in combination with VP-16 and cytarabine, for induction/consolidation therapy, followed by autologous stem cell transplantation (ASCT) in elderly patients with acute myeloid leukaemia (AML).

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INTRODUCTION

The outcome of chemotherapy in elderly patients with AML is generally poor, with complete remission (CR) rates around 50%, and generally less than 10% of patients alive after 3 years. Idarubicin and mitoxantrone have shown superiority over conventional anthracyclines in several randomised trials [1, 2]. The addition of etoposide (VP16) to cytarabine (ara-C) and anthracyclines has been shown to prolong disease-free survival (DFS) in an Australian randomised trial [3]. Also, in young patients, a post-induction myeloablative regimen followed by (ASCT) reduces relapse rate [4]. We have therefore studied the outcome of combining both of these approaches in elderly AML patients, using reduced doses of the cytotoxic agents.

PATIENTS AND METHODS

Eligibility criteria included age over 60 years; a new diagnosis of AML, either *de novo* or secondary to myelodysplasia or toxic exposure; WHO performance status of 1 or 2; and no major organ failure. Patients were randomised to induction chemotherapy with idarubicin (8 mg/m²/day, i.v., at days 1, 3 and 5) or mitoxantrone (7 mg/m²/day, i.v., at days 1, 3 and 5), both combined with VP16 (100 mg/m²/day, i.v., on days 1 to 3) and ara-C (100 mg/m²/day, as a continuous infusion on days 1 to 7). In all patients older than 70 years, and in some younger patients, G-CSF (Filgrastim) was used at a dose of 5 µg/kg/day from the day after the end of the chemotherapy (day 8) until recovery from neutropenia.

One or two courses of induction chemotherapy were given, until CR had been achieved. Consolidation chemotherapy involved only one course, which was administered as soon as CR was reached, at the same dosages as for induction, except that ara-C was administered on only 5 days.

ASCT could be offered to some patients within 6 weeks of haematological recovery after the first consolidation. Eligibility criteria included age under 70 years (increased to 75 years in April 1994) and a WHO performance status of 0 or 1 after the first consolidation.

The peripheral blood stem cell (PBSC) harvest was carried out with G-CSF (5 µg/kg/day for 7 days), administered after recovery from the first consolidation.

Conditioning was carried out with several different agents: initially, BCNU (800 mg/m²) alone, then busulfan (4 mg/kg for 4 days) alone, and finally BAVC (BCNU, 800 mg/m²; AMSA, 150 mg/m² x 3; VP-16, 150 mg/m² x 3; and ara-C, 300 mg/m² x 3). G-CSF (5 µg/kg/day) was administered after transplantation.

A total of 158 patients were entered into the trial, with a median age of 69 years. Of these, 116 had primary AML and 42 had either secondary AML or transformed primary myelodysplastic syndrome. Disease was extramedullary in 45 patients. Haematological characteristics were unremarkable; there were no FAB subtype M3 (acute promyelocytic leukaemia) patients, because they were treated in another trial. AML was unclassifiable in 23 patients, mainly those with secondary AML.

RESULTS

Efficacy of induction

For the purposes of analysis, 4 patients who died during the 7 days of induction chemotherapy were not evaluated for efficacy of induction (Table 1). Of the remaining 154 patients, 61% achieved CR, including 59% in the idarubicin arm and 63% in the mitoxantrone arm, a difference which is not significant. 30% of patients had resistant disease and 9% suffered toxic death. In 10 patients, CR required two courses of induction.

Looking further at these data, we divided the patients who achieved CR into sub-groups on the basis of *de novo* AML and age. CR was achieved in 65% of cases with *de novo* AML, compared with 50% in other patients, a difference

Efficacy of induction therapy.				
Chemotherapy	No. of patients	Complete remission (%)	Toxic death (%)	Resistant disease (%)
Idarubicin	75	44(59%)	26	5
Mitoxantrone	79	50(63%)	20	9
Totals	158	94(61%)	46(30%)	14(9%)

Table 1.

that was not significant ($p = 0.12$). However, division into age groups just reached significance ($p = 0.05$), with 68% of those under 70 years of age achieving CR, compared with 52% of the older ones.

Haematological toxicity

Data for haematological toxicity for induction and consolidation therapy are shown in Table 2. There were no significant differences between the idarubicin and mitoxantrone arms of the study. The haematological toxicity of consolidation therapy was slightly less than that of induction.

Haematological toxicity.	Induction		Consolidation	
	Idarubicin (n=26)	Mitoxantrone (n=24)	Idarubicin (n=23)	Idarubicin (n=24)
Neutropenia (PMN $< 0.5 \times 10^9/L$)	26(10-46)	24(9-56)	23(45-42)	24(44-59)
Thrombocytopenia ($< 50 \times 10^9/L$)	25(13-57)	24(13-79)	25(16-63)	22(13-47)

Table 2.

Non-haematological toxicity

During the first course of induction chemotherapy the main toxicity was due to fever and infection, which accounted for most of the toxic deaths, with no significant differences between the two arms. Diarrhoea with necrotising enterocolitis lead to one death in the idarubicin arm. The non-haematological toxicity of consolidation was similar to that of induction, with 7 deaths in 74 patients.

Autologous transplantation

A total of 19 patients were selected for autologous transplantation, with a median age of 67 years (61-74 years). They all received PBSC, with the exception of one patient who received bone marrow. Median values of quantities of the cells received were 7.3×10^8 mononuclear cells/kg (range 1.5-15.3), 29.2×10^4 CFU-GM cells/kg (range 5.2-150) and 90×10^8 CD34+ cells/kg (range 3.6-126.6). Conditioning was with BCNU in 6 patients, busulfan in 9 and BAVC in 4.

All but one of the transplants were performed in Lyon, where we saw during this period 36 patients who were eligible on grounds of age. Of these, 2 refused further treatment, 4 were excluded on practical grounds, 4 had an inadequate PBSC harvest and 8 had significant toxicity following the first consolidation, or relapsed before transplantation.

Engraftment was relatively rapid, with neutropenia ($< 0.5 \times 10^9/L$) for a median of 7 days (range 2-13 days) and thrombocytopenia ($< 50 \times 10^9/L$) for a median of 18 days (range 0 to 180 days), though 6 patients never reached this level and 3 were dependent on platelet transfusions until relapse. There were 2 toxic deaths due to infection. Mean hospitalisation was 22 days (range 11-32 days).

Follow-up

The median follow-up of these patients is 11 months. Ten patients died while in CR: 1 after induction, 7 from toxicity after consolidation and 2 after autografting. 12 of 15 patients autografted after conditioning with BCNU or busulfan, have relapsed, as has 1 of 4 conditioned with BAVC, at a median of 5 months after transplantation (range 2-15 months).

There were no differences in the survival curves of the idarubicin and the mitoxantrone arms of the study.

CONCLUSIONS

Both arms of the regimen used in this trial induced a high rate of CR, particularly with *de novo* AML, even in patients aged over 70 years of age. Early relapse could not be prevented by one course of consolidation. ASCT after myeloablative therapy could be performed in selected patients up to the age of 75 years. However, a reduced-dose conditioning regimen with BCNU or busulfan alone did not prevent early relapse.

REFERENCES

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