Letters to the Editor

Acute Myeloid Leukemia

Comparison of BAVC and BuCy regimens in autologous stem cell transplantation for adult patients with acute myeloid leukemia

This retrospective registry study compared the BAVC regimen to the BuCy regimen in autologous transplants for acute myeloid leukemia and showed that the two regimens provided a similar outcome. Relapse incidence was higher and transplant related mortality lower with BAVC. The study indicates that BAVC may offer a good alternative to BuCy.

haematologica 2004; 89:107-108
(*http://www.haematologica.org/journal/2004/1/107*)

Autologous stem cell transplantation (ASCT) improves the survival of patients with acute myeloid leukemia (AML).[1] Total body irradiation (TBI) has frequently been part of the conditioning regimen in association with high dose chemotherapy.[2] However, because of late effects, preparative regimens using high dose chemotherapy alone have been tested. Combinations of busulfan with cyclophosphamide (BuCy)[3,4] were reported to be effective, although toxicity still occurred. In an attempt to reduce toxicity, the BAVC regimen was introduced.[5,6] Until now there are no data showing the real efficacy of the BAVC regimen on long-term survival. We, therefore, retrospectively compared BAVC and BuCy in order to evaluate the long term antileukemic effect of BAVC.

Adult patients (> 16 years old) with AML receiving either the BAVC regimen (BCNU 800 mg/m^2, amsacrine 150 mg/m^2/day for 3 days, VP-16 150 mg/m^2/day for 3 days and ara-C 300 mg/m^2/day for 3 days) or the reduced BuCy regimen (busulfan 4 mg/kg/day for 4 days and cyclophosphamide 60 mg/kg/day for 2 days) and autologous stem cell transplantation (ASCT) in first complete remission (CR1) were selected. All patients had been reported to the European Group for Blood and Marrow Transplantation (EBMT) registry and received an ASCT between January 1984 and December 2002. Transplant-related mortality (TRM) was defined as death of non-leukemic causes; relapse incidence (RI) was defined on the basis of cytological relapse and leukemia-free survival (LFS) as the time interval between the transplant and first event (either relapse or death in CR).

The following variables were analyzed: regimen (BAVC or BuCy), age, time from diagnosis to CR1, time from CR1 to transplant, French American British (FAB) classification, gender, source of stem cells and leukocyte count at diagnosis.

To compare the 2 groups, those prepared with BAVC and those with BuCy, we used the χ^2 test for categorical variables and the non-parametric Mann-Witney U test for continuous variables. Patients were censored from analysis at the time of relapse or at the last follow-up.[7] The probability of overall survival (OS) and LFS was estimated by the product-limit method.[8] The significance of differences between curves was estimated by the log-rank test (Mantel-Cox). All variables were included in a Cox proportional hazard model.[9] RI and TRM were events which competed with each other. Accordingly, estimations of the incidence of these events relied on the non parametric estimator of cumulative incidence curves, while predictive analyses were based on the proportional hazard model for these subdistributions of competing risks.[10] These analyses were performed using the *cmprsk* package (developed by Gray, June, 2001) on Splus 2000 software and SPSS software. A total of 526 patients with AML in CR1 were identified; 94 had received BAVC and 432 BuCy. The comparison of the distribution between the two regimens is shown in Table 1. The median follow-up was 89 months (1-213) for BAVC, and 59 months (1-158) for BuCy. The comparison of 5-year outcomes in the patients treated with BAVC and BuCy showed a LFS of 37±5% and 46±2% (p = 0.23) (Figure 1), a RI of 58±11% and 44±5% (p = 0.015) (Figure 2), a TRM of 4±4% and 11±3% (p = 0.04) and an OS of 47±5% and 50±2% (p = 0.85), respectively.

Table 1. Comparison of the characteristics of adult patients with acute myeloid leukemia who received either the BAVC regimen or the BuCy regimen in first complete remission.

	BuCy (n=432)	*BAVC (n=94)*	*p*
Gender (male/female)	218/214	50/44	0.64
Median age	38 years (16-71)	41 years (17-68)	< 0.01
Leukocyte count at diagnosis	14.4×10^9/L (0.2-276)	9.1×10^9/L (0.8-117)	0.16
FAB classification			
M1	13 %	13 %	
M2	32 %	30 %	global
M3	6 %	13 %	*p* value:
M4	29 %	22 %	0.15
M5	15 %	14 %	
M6	4 %	7 %	
M7	1 %	1 %	
Median time from diagnosis to CR1	39 days (14-424)	38 days (16-168)	0.83
Median time from CR1 to ASCT	132 days (15-681)	128 days (21-520)	0.5
Source of stem cells			
Bone marrow	75 %	81 %	0.04
Peripheral blood	25 %	19 %	
Median year of ASCT	1994	1991	< 10^{-4}

Multivariate analysis (Table 2) showed that times from diagnosis to CR1, from CR1 to ASCT, and year of ASCT were prognostic factors for outcome. The conditioning regimen, BAVC or BuCy, did not influence survival. No interaction was observed between these two conditioning regimens and prognostic factors identified by multivariate analysis.

This study shows that patients with AML who received BAVC and ASCT had an identical survival to that of patients receiving BuCy. However, patients treated with BAVC had a higher RI of 58±11% but a lower TRM of only 4±4%. These results confirm the low toxicity of the BAVC regimen that

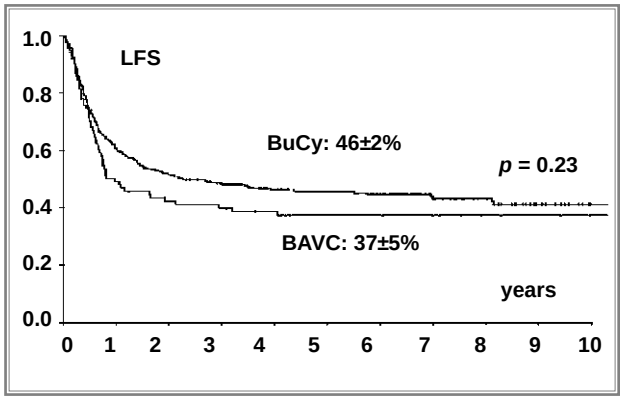

Figure 1. Comparison of leukemia-free survival (LFS) at 5 years in adult patients with acute myeloid leukemia in first complete remission, treated with the BAVC regimen or the BuCy regimen. Results show no statistical difference between LFS induced by the two regimens.

Table 2. Multivariate analysis. Prognostic factors.

	Variables	*p*	*RR*
LFS	Time from diagnosis to CR1 <39 days*	0.006	0.68 [0.51-0.89]
	Time from CR1 to ASCT > 132 days*	0.046	0.73 [0.57-0.99]
	Year of transplant > 1993*	0.023	0.64 [0.43-0.94]
RI	Time from diagnosis to CR1 < 39 days*	0.01	0.72 [0.52-0.99]
OS	Time from diagnosis to CR1 < 39 days*	0.014	0.69 [0.51-0.92]
	Time from CR1 to ASCT > 132 days*	0.02	0.70 [0.52-0.95]
	Year of transplant > 1993*	0.023	0.61 [0.41-0.93]

**median values.*

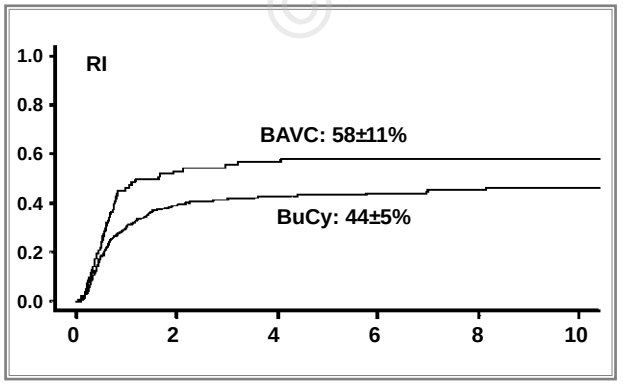

Figure 2. Comparison of relapse incidence (RI) at 5 years in adult patients with acute myeloid leukemia in first complete remission treated with the BAVC regimen or the BuCy regimen. A higher RI is observed among patients treated with the BAVC regimen.

had already been reported by the Rome team.[5,6] In our study, this low TRM is not explained by the source of stem cells because the number of patients who received a peripheral blood transplant was lower among those treated with BAVC. Nor is it explained by the age of patients since patients in the BAVC group were older. A center effect cannot be excluded. However BAVC use was reported by 12 centers (52% from Rome) and BuCy by 69 centers (22% from the same center in Rome). Unfortunately cytogenetic abnormalities at diagnosis could not be studied and we cannot exclude that there was a difference in the distribution of cytogenetic risk groups between the patients treated with BAVC or BuCy.

Although it cannot be concluded from this retrospective study that BAVC should replace BuCy, the low TRM observed with BAVC indicates that when BuCy or even TBI cannot be given, considering the patient's age and physical conditions, BAVC may offer a good alternative.

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Key words: BAVC, autologous transplants, acute myeloid leukemia.

References

1. Gorin NC. Autologous stem cell transplantation in acute myelocytic leukemia. Blood 1998;92:1073-90.
2. Thomas ED, Storb R, Clift RA, Fefer A, Johnson L, Neiman PE, et al. Bone marrow transplantation I and II. N Engl J Med 1975;292: 895-902.
3. Santos GW, Tuschka PJ, Brookmeyer R, Saral R, Beschorner WE, Bias W, et al. Marrow transplantation for acute nonlymphocytic leukemia after treatment with busulfan and cyclosphosphamide. N Engl J Med 1983;309:1347-53.
4. Tutschka PJ, Copelan EA, Klein JP. Bone marrow transplantation following a new busulfan and cyclophosphamide regimen. Blood 1987;70:1382-8.
5. Meloni G, de Fabritiis P, Petti MC, Mandelli F. BAVC regimen and autologous bone marrow transplantation in patients with acute myelogenous leukemia in second remission. Blood 1990;75: 2282-5.
6. Meloni G, Vignetti M, Avvisati G, Capria S, Micozzi A, Giona F. BAVC regimen and autograft for acute myelogenous leukemia in second complete remission. Bone Marrow Transplant 1996;18: 693-8.
7. Clift R, Goldman LM, Gratwohl A, Horowitz M. Proposal for standardized reporting of bone marrow transplantation for leukemia. Bone Marrow Transplant 1989;4:445-8.
8. Kaplan EL, Meier P. Non parametric estimation from incomplete observations. J Am Stat Assoc 1958;53:457-81.
9. Cox DR. Regression models and life tables. J R Stat Soc 1972;34: 187-202.
10. Fine JP, Gray RJ. A proportional hazard model for the subdistribution of a competing risk. J Am Stat Assoc 1999;94:496-509.