Etoposide plus cytarabine versus cyclophosphamide or melphalan in busulfan-based preparative regimens for autologous stem cell transplantation in adults with acute myeloid leukemia in first complete remission: A study from the Acute Leukemia Working Party of the EBMT

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Abstract

Introduction

High-dose myeloablative chemotherapy followed by autologous stem cell transplantation (ASCT) is a valid treatment option for patients with acute myeloid leukemia (AML) in first complete remission (CR1). However, information on specific conditioning regimens is scarce. The ALWP showed improved outcomes with busulfan and high-dose melphalan (BUMEL) conditioning compared to busulfan with cyclophosphamide (BUCY) in high-risk patients. The combination of more AML directed drugs using high-dose cytarabine, etoposide and busulfan (BEA) has been the recommended regimen in subsequent PETHEMA studies.

Methods

In order to analyse the impact of the conditioning regimen we retrospectively compared the outcome of adult patients with AML in CR1 that received an ASCT from 2010 to 2021 with either BEA, BUCY or BUMEL registered in the EBMT database.

Results

Overall 1560 patients underwent ASCT at a median age of 52 years (range, 18–75). Eight hundred and forty-three (54%) were male. Two hundred and sixty-seven (23%), 815 (70%) and 75 (7%) had favorable-, intermediate- and adverse-risk cytogenetics, respectively (data not reported for 403 patients). FLT3-ITD and NPM1 mutations were present in 177 (23%) and 481 (58%) patients, respectively. Regarding conditioning, 156, 1143 and 261 received BEA, BUCY and BUMEL, respectively. Compared to BUCY and BUMEL, BEA patients were younger ($p < 0.001$) and less frequently had NPM1 mutations ($p = 0.03$). Transplant outcomes at 5 years with BEA, BUCY and BUMEL were: cumulative incidence of relapse 41.8%, 46.6% and 51.6%; non-relapse mortality (NRM) 1.5%, 5.2% and 7.3%; probability of leukemia-free survival (LFS) 56.7%, 48.2% and 41.1%; and overall survival (OS) 71.3%, 62.3% and 56%, respectively. In multivariable analysis the BEA regimen showed significant improvement in OS compared to BUCY (hazard ratio [HR] 0.65; 95% CI, 0.42–0.83; $p = 0.048$) and BUMEL (HR 0.59; 95% CI, 0.37–0.94; $p = 0.029$). Favorable cytogenetics and younger age were also associated with improved OS.

Conclusions

High-dose myeloablative combination chemotherapy with BEA offered improved outcomes compared to classical BUCY or BUMEL in patients with AML in CR1 undergoing ASCT.

INTRODUCTION

The role of autologous stem cell transplantation (ASCT) as consolidation therapy for patients with acute myeloid leukemia (AML) in first complete remission (CR1) has constantly changed with advances in

prognosis, risk-adapted treatment, and allogeneic transplantation. Currently, ASCT continues to be a therapeutic option mainly used for patients with favorable and intermediate-risk AML.[1,2]

Among the factors that can determine the efficacy and safety of ASCT, measurable residual disease (MRD) status and conditioning regimen are probably the most important. Regarding the latter, the most common conditioning regimen for ASCT in AML is the combination of busulfan with cyclophosphamide (BUCY). Recently, two retrospective studies of the Acute Leukemia Working Party (ALWP) of the European Society for Blood and Marrow Transplantation (EBMT) have compared the results in patients with AML in CR1 who received BUCY as a conditioning regimen for ASCT with those who received a combination of busulfan with high-dose melphalan (140 mg/m^2) (BUMEL). The first preliminary study in 853 patients autografted from 2005 to 2013 showed that the incidence of relapse, leukemia-free survival (LFS), and overall survival (OS) was better with BUMEL, while non-relapse mortality (NRM) was similar in both groups.[3] However, in a subsequent larger study in 1649 patients autografted from 2000 to 2016,[4] an interaction between conditioning regimen and cytogenetic risk category was detected, showing that only the poor-risk group benefited from the use of BUMEL, while no differences were confirmed in the other cytogenetic risk categories.

Following encouraging preliminary results,[5,6] another alternative to the classic BUCY regimen, replacing cyclophosphamide with etoposide and high-dose cytarabine (BEA regimen), along with granulocyte colony-stimulating factor (G-CSF) priming, has been increasingly used in patients with AML in CR1.[7–9] The promising results reported with BEA prompted us to compare the safety and efficacy of BEA, BUMEL, and BUCY as preparative regimens for ASCT in patients with AML in CR1, registered in the EBMT database.

PATIENTS AND METHODS

Study design and data source

This is a retrospective registry-based analysis on behalf of the ALWP of the EBMT. The latter is a voluntary working group of more than 650 transplantation centers that are required to report all consecutive stem cell transplantations and follow ups once a year. The EBMT registry has internal quality control regarding accuracy and consistency of the entered data and regular queries on missing/incorrect data and follow-up requests are performed. All transplantation centers are required to obtain written informed consent before data registration with the EBMT in accordance with the 1975 Declaration of Helsinki guidelines. The ALWP of the EBMT approved this study.

Patients and conditioning regimens

Eligibility criteria for this analysis included adult patients (aged > 18 years) with *de novo* AML who underwent an ASCT in CR1 after receiving a preparative regimen consisting of either BUCY, BUMEL or BEA, and who were reported to the EBMT registry from January 2010 to December 2021.

Across conditioning regimens, busulfan was administered either intravenously (IV) for a total dose of 9.6 mg/kg or 12.8 mg/kg or orally for a total dose of 12 mg/kg or 16 mg/kg over 3–4 days. Busulfan was combined either with cyclophosphamide 60 mg/kg daily for 2 days (BUCY), melphalan administered as a single IV dose of 120 mg/m^2 or 140 mg/m^2 (BUMEL), or etoposide given at a dose of 20 mg/kg/day on days − 4 and − 3, cytarabine 3 g/m^2/12 h on days − 3 and − 2 (BEA), and G-CSF 10 µg/kg/day between days − 9 and − 2 as priming to increase the chemosensitivity of residual leukemic cells to cytarabine.

Endpoints and definitions

The primary end points of this study were LFS and OS. Secondary endpoints included disease relapse incidence and NRM. OS was defined as the time between the date of transplant and death. LFS was defined as survival without relapse or progression, and was calculated until the date of first relapse, death from any cause, or the last follow-up. Relapse was defined as disease recurrence and appearance of blasts in the peripheral blood or bone marrow (> 5%) after CR. NRM was defined as death without previous relapse.

Statistical Analysis

Patient-, disease-, and transplantation-related characteristics were compared between the three groups that received either BUCY, BUMEL or BEA, using the chi-squared test for categorical variables and the Kruskal-Wallis test for continuous variables. The variables considered were patient age at transplantation, sex, Karnofsky score, interval from diagnosis to transplantation, cytogenetics risk group,[10] presence of NPM1 and FLT3-ITD mutations, year of transplantation, and preparative regimen (BUCY, BUMEL, or BEA). Cumulative incidence functions were used to estimate relapse incidence, and NRM.[11,12] Competing risks were death for relapse incidence and relapse for NRM. Probabilities of LFS and OS were calculated using Kaplan-Meier estimates.[13] Survival probabilities are given at 2 and 5 years as percentages with 95% confidence intervals (CIs). The follow-up time was calculated using the reverse Kaplan–Meier method Univariate analyses were performed using the log-rank test for LFS and OS, and Gray's test for cumulative incidence. All variables that were significantly different between the three groups and/or were known to be prognostic factors were included in multivariate analyses using the Cox proportional-hazards model.[14] To test for a center effect, we introduced a random effect or 'frailty' for each center into the model.[15] The significance level was fixed at 0.05, and p values were two-sided. Statistical analyses were performed using the R statistical software version 4.0.2 (R Foundation for Statistical Computing, Austria, Vienna; available online at http://www.R-project.org).

RESULTS

Patient and Transplantation Characteristics

The study included a total of 1560 patients, of whom 1143 (73%) received BUCY, 261 (17%) received BUMEL, and 156 (10%) received BEA. The median follow-up was 51.0 months (interquartile range [IQR], 47.6-55.0), 43.0 months (IQR, 37.3-48.0), and 49.0 months (IQR, 40.7-58.7) for BUCY, BUMEL, and BEA,

respectively. The distribution of patient and disease characteristics is shown in Table 1. Patients who received BEA were younger and harbored a lower proportion of NPM1 mutations than those who received BUCY or BUMEL. There were no other significant differences.

Relapse

The median time to relapse was 7.9 months (range 1-108). The 5-year cumulative incidence of relapse for the entire cohort was 46.9% (95% CI, 44–49.7) and it was not significantly different across the conditioning regimens with 41.8% (95% CI, 32.9–50.4) for BEA, 46.6% (95% CI, 43.3–49.9) for BUCY, and 51.6% (95% CI, 44.1–58.6) for BUMEL (p=0.12) (Table 2, Figure 1A). On multivariable analysis, conditioning regimen was not significantly associated with the incidence of relapse (Table 3). Favorable cytogenetics was the only factor significantly associated with relapse (HR, 0.46; 95% CI, 0.35-0.61; p<0.0001), results not shown.

NRM and cause of death

The 5-year cumulative incidence of NRM was 1.5% (95% CI, 0.3–5.1) for BEA, 5.2% (95% CI, 3.9–6.8) for BUCY, and 7.3% (95% CI, 4.3–11.3) for BUMEL (p=0.11) (Table 2, Figure 1B). On multivariable analysis, conditioning regimen was not significantly associated with the risk of NRM (Table 3). Age per 10 years (HR 1.89; 95% CI 1.46–2.45; p=0.001) was the only factor significantly associated with an increased NRM, result not shown. Causes of death are shown in Table 4.

Survival outcomes

The overall 5-year LFS and OS were 47.9% (95% CI, 45–50.8) and 62.3% (95% CI, 59.3–65.1), respectively. With respect to conditioning regimen, LFS and OS were 56,7% (95% CI, 47.4–64.9) and 71.3% (95% CI, 61.8–78.8) for BEA, 48.2% (95% CI, 44.8–51.5) and 62.3.1% (95% CI, 58.9–65.6) for BUCY, and 41.1% (95% CI, 33.9–48.2) and 56% (95% CI, 48.1–63.3) for BUMEL (p=0.01 and p=0.005), respectively (Table 2, Figure 1C and 1D).

On multivariable analysis, favorable cytogenetics was the only statistically significant factor associated with improved LFS (HR, 0.46; 95% CI, 0.35-0.61; p<0.0001). Regarding OS, BEA conditioning was significantly associated with improved OS compared to BUCY (HR, 0.65; 95% CI, 0.42-1; p=0.048) and BUMEL (HR, 0.59; 95% CI, 0.37-0.94; p=0.029) (Table 3). Older patient age per 10 years (HR, 1.18; 95% CI, 1.09-1.28; p<0.001) was associated with a lower OS and favorable cytogenetics (HR, 0.44; 95% CI, 0.31-0.62; p<0.001) was significantly associated with better OS.

DISCUSSION

This study shows that the conditioning regimen BEA, which combines busulfan, etoposide, high-dose cytarabine, and G-CSF priming, results in better survival than BUCY and BUMEL in patients autografted for AML in CR1. Cytogenetics remains the most important prognostic factor with low survival probability for high-risk patients.

Although the use of ASCT for AML has declined over the years,[16] it is still an effective and widely used procedure for low- and intermediate-risk disease that allows the administration of myeloablative chemotherapy in an effort to prevent relapse. Therefore, the choice of the most optimal conditioning that combines the highest efficacy with low toxicity is a fundamental goal for clinical research in this field. Since prospective randomized trials are unlikely to be conducted in this setting, it is necessary to rely on well-collected retrospective data, well-designed statistical analysis and cautious interpretation to avoid potential bias. In this large retrospective registry-based study, all patients included in the analysis had AML in CR1 and had received ASCT recently with enough follow-up to draw meaningful conclusions. Most patients had available cytogenetic and basic molecular data to stratify the disease risk. However, another important factor, such as MRD status at transplant, was not available and its impact should be assessed in future studies.

Overall, patient and disease characteristics were well balanced between the three conditioning groups. Patients receiving BEA were younger, although the difference (median age 1-4 years) was small and does not seem clinically important. In contrast, a lower proportion of patients in the BEA group had NPM1 mutations, a marker of good prognosis that provides excellent survival rates after ASCT.[17] As expected for patients transplanted in recent years with risk-adapted protocols, the majority of evaluable patients had favorable- or intermediate-risk cytogenetics and 75% of patients were FLT3-ITD negative (as per the 2010 European LeukemiaNet [ELN] classification).

We observed a relatively good survival of the entire cohort, with a long-term LFS of around 50% and OS of over 60%, which seems better than that reported in previous studies,[18,19] and similar to the most recently published data.[3,20–23]

ASCT is generally perceived as a very low-risk procedure. However, in AML, a non-negligible incidence of NRM of around 5% has been reported recently,[4,17,22–24] as was observed in our study in patients receiving BUCY or BUMEL. However, we should highlight a considerably lower NRM in patients who received BEA (0.6% at 2 years and 1.5% at 5 years), confirming previous results with this conditioning regimen.[5,7,8] Replacement of the alkylating agents cyclophosphamide and melphalan with more specific AML drugs, such as the topoisomerase inhibitor etoposide and the DNA polymerase inhibitor cytarabine, could have led to reduced toxicity.

The most frequent cause of death was relapse, which was driven mainly by the genetic abnormalities. This is expected in ASCT where allo-SCT is reserved for salvage treatment. In fact, around half of the patients that relapsed in our study were able to undergo subsequently allo-SCT. In the era of targeted therapy, where more patients can achieve a deeper response before transplant and considering post-transplant maintenance strategies, it is likely that the relapse rate can be decreased in this setting. The BEA regimen provided high antileukemic efficacy, at least similar to that obtained with BUCY and BUMEL.

The most important finding of our study is that patients who received BEA showed a better survival than those receiving BUCY or BUMEL, probably due to a combination of factors that individually were not

statistically significant (NRM and relapse), but together, had a significant impact on survival. Whether or not some specific cytogenetic risk category patients could benefit from one conditioning regimen over another, as previously shown with BUMEL compared to BUCY in high-risk patients,[4] could not be evaluated in the present study due to the relatively low number of patients in the BEA group.

In conclusion, the choice of conditioning for patients autografted for AML in CR1 is relevant. A BEA regimen provides better survival and challenges the standard of care with BUCY or BUMEL. Selection of patients with more favorable cytogenetics and new methods to decrease the post-transplant relapse rate are needed to further improve outcomes after ASCT in AML.

Declarations

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

AUTHOR CONTRIBUTIONS

Jaime Sanz, Norbert Claude Gorin, Mohamad Mohty and Fabio Ciceri: designed the study. Myriam Labopin: performed statistical analysis and helped with the interpretation of the results. Jaime Sanz: wrote the manuscript. Michael Daskalakis, A.E.C. Broers, Gwendolyn Van Gorkom, Ellen Meijer, Tobias Gedde-Dahl, Juan Montoro, William Arcese, Jose Antonio Pérez-Simón, N. Schaap, Johan Maertens, Radovan Vrhovac, Francesco Lanza: provided patients for the study. All authors edited and approved the manuscript.

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Tables

Table 1. Patient and disease characteristics

	Overall	BEA	BUMEL	BUCY	p
No. of patients	1560	156	261	1143	
Age, yrs, median (range)	52 (18-86)	51 (19-71)	55 (18-73)	52 (18-86)	0.0005
IQR	41-60	40-59	44-62	41-59	
Year of transplant, median (range)	2015 (2010-2021)	2014 (2010-2021)	2013 (2010-2021)	2015 (2010-2021)	< 0.0001
Gender, n (%)					
Male	843 (54.1)	87 (56.1)	148 (56.9)	608 (53.2)	0.48
Female	715 (45.9)	68 (43.9)	112 (43.1)	535 (46.8)	
missing	2	1	1	0	
Karnofsky score, n (%)					
<90	239 (16.4)	176 (16.5)	47 (18.3)	16 (12)	0.28
>=90	1216 (83.6)	889 (83.5)	210 (81.7)	117 (88)	
missing	105	78	4	23	
Cytogenetics, n (%)					
Favorable	267 (17.1)	37 (23.7)	32 (12.3)	198 (17.3)	0.61
Intermediate	815 (52.2)	74 (47.4)	124 (47.5)	617 (54)	
Adverse	75 (4.8)	3 (1.9)	25 (9.6)	47 (4.1)	
NA/failed	403 (25.8)	42 (26.9)	80 (30.7)	281 (24.6)	
FLT3, n (%)					
FLT3 not mutated	602 (77.3)	79 (83.2)	91 (78.4)	432 (76.1)	0.29
FLT3-ITD	177 (22.7)	16 (16.8)	25 (21.6)	136 (23.9)	
missing	781	61	145	575	

NPM1, n (%)					
NPM1 not mutated	349 (42)	53 (54.6)	48 (39.7)	248 (40.5)	0.028
NPM1 mutated	481 (58)	44 (45.4)	73 (60.3)	364 (59.5)	
missing	730	59	140	531	
Subsequent allo-SCT, n (%)					
No	1251 (80.2)	125 (80.1)	212 (81.2)	914 (80)	0.90
Yes	309 (19.8)	31 (19.9)	49 (18.8)	229 (20)	
Follow-up, months, median (IQR)	48.8 (46.5-52.7)	49.0 (40.7-58.7)	43.0 (38.3-48.0)	51.0 [47.6-55.0]	0.27

Abbreviations:

Table 2. Univariable analysis of transplant outcomes according to conditioning regimen

Outcome*, % (95% CI)	Overall	BEA	BUMEL	BUCY	p
RI	46.9 (44 - 49.7)	41.8 (32.9 - 50.4)	51.6 (44.1 - 58.6)	46.6 (43.3 - 49.9)	0.12
NRM	5.2 (4.1 - 6.5)	1.5 (0.3 - 5.1)	7.3 (4.3 - 11.3)	5.2 (3.9 - 6.8)	0.11
LFS	47.9 (45 - 50.8)	56.7 (47.4 - 64.9)	41.1 (33.9 - 48.2)	48.2 (44.8 - 51.5)	0.01
OS	62.3 (59.3 - 65.1)	71.3 (61.8 - 78.8)	56 (48.1 - 63.3)	62.3 (58.9 - 65.6)	0.005
Subsequent allo-SCT	25 (22.5 - 27.5)	26 (18.3 - 34.2)	25.1 (19.1 - 31.7)	24.9 (22 - 27.8)	0.93

* NRM and RI: cumulative incidence at 5 years; DFS and OS: survival probability at 5 years.

Abbreviations: CI, confidence interval; NRM, non-relapse mortality; RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival; allo-SCT, allogeneic stem cell transplant

Table 3. Multivariable analysis of transplants outcomes according to conditioning regimen

	BEA vs BUMEL			BEA vs BUCY			BUMEL *vs* BUCY		
Outcome	HR	95% CI	p	HR	95% CI	p	HR	95% CI	p
NRM	0,37	0,10-1,37	0.14	0.42	0.12-1.43	0.16	0.89	0.48-1.64	0.72
RI	0,76	0,51-1,16	0.21	0.81	0.56-1.18	0.28	0.94	0.73-1.20	0.65
LFS	0,73	0,49-1,09	0.12	0.78	0.55-1.11	0.17	0.93	0.74-1.18	0.58
OS	**0.59**	**0.37-0.94**	**0.029**	**0.65**	**0.42-1**	**0.048**	0.92	0.70-1.19	0.52

Abbreviations: CI, confidence interval; HR, hazard ratio; NRM, non-relapse mortality; RI, relapse incidence; LFS, leukemia-free survival; OS, overall survival

Table 4. Cause of death according to conditioning regimen

Cause of death	Overall (n=484)	BEA (n=35)	BUMEL (n=92)	BUCY (n=357)
Relapse	312 (66.4%)	23 (67.7%)	57 (66.3%)	232 (66.3%)
Infection	71 (15.1%)	5 (14.7%)	10 (11.6%)	56 (16%)
Cardiac toxicity	1 (0.2%)	0 (0%)	0 (0%)	1 (0.3%)
Hemorrhage	4 (0.9%)	0 (0%)	1 (1.2%)	3 (0.9%)
Failure/Rejection	2 (0.4%)	0 (0%)	1 (1.2%)	1 (0.3%)
Sinusoidal obstruction syndrome	5 (1.1%)	1 (2.9%)	1 (1.2%)	3 (0.9%)
Interstitial pneumonitis	5 (1.1%)	0 (0%)	1 (1.2%)	4 (1.1%)
Secondary malignancy	15 (3.2%)	3 (8.8%)	3 (3.5%)	9 (2.6%)
Multiorgan failure	5 (1.1%)	0 (0%)	1 (1.2%)	4 (1.1%)
CNS toxicity	1 (0.2%)	0 (0%)	1 (1.2%)	0 (0%)
Other	48 (10.2%)	2 (5.9%)	10 (11.6%)	37 (10.6%)
Missing	14	1	6	7

Figures

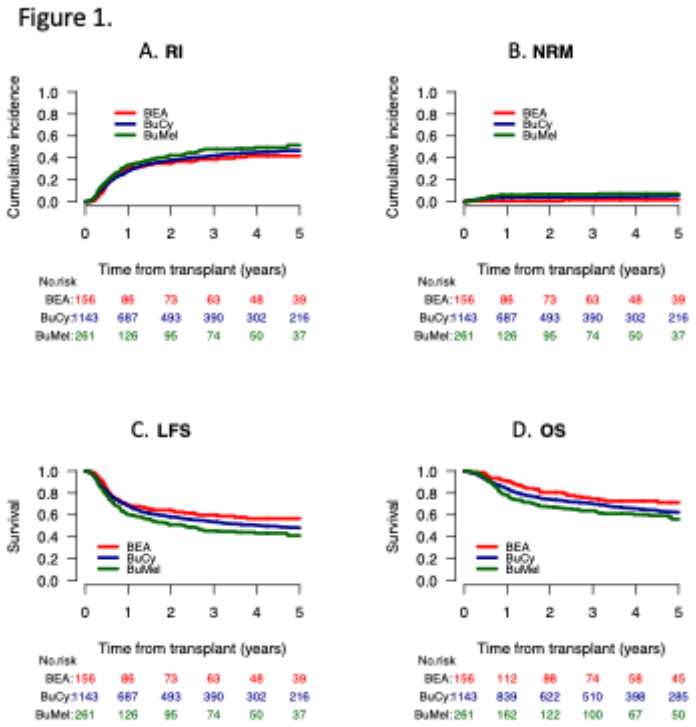

Figure 1

Autologous stem cell transplant outcomes for patients receiving conditioning with either BEA, BUCY or BUMEL: (A) Cumulative incidence of relapse (RI); (B) Cumulative incidence of non-relapse mortality (NRM); (C) Probability of leukemia-free survival (LFS); (D) Probability of overall survival (OS).