aGvHD, cGvHD

The comparison of reduced-intensity stem cell transplantation conditioning regimens in patients with high-risk AML

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For many patients with hematological malignancies, like acute myeloid leukemia (AML), with poor outcome prognosis, allogeneic stem cell transplantation (allo-SCT) at first remission (CR1) is a common treatment strategy.[1] However, allo-SCT is associated with significant non-relapse mortality (NRM) when combined with traditional myeloablative conditioning regimens. Conventional myeloablation is based on high intensity busulfan (Bu) or total body irradiation (TBI) in combination with cyclophosphamide (Cy).[1,2] To reduce the risk of toxicity, reduced-intensity or non-myeloablative conditioning regimens have been developed. Nevertheless, these are not as efficient in reducing disease recurrence. To find the right balance between efficacy and safety, reduced toxicity regimens using Bu or TBI at moderate doses together with fludarabine (Flu) have been proposed.[1,2]

During the 61st American Society of Hematology Annual Meeting & Exposition on Monday 9th December 2019, Sebastian Giebel from Maria Skłodowska Curie Memorial Cancer Centre and Institute of Oncology, Warsaw, PL, presented the results of a retrospective study by the Acute Leukaemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT) that compared reduced toxicity Bu/Flu to similar intensity TBI/Flu in patients with AML who were treated with allo-SCT. The primary endpoint of this study was leukemia-free survival (LFS), while the key secondary objectives included, NRM, relapse incidence (RI), overall survival (OS), and graft-*versus*-host disease (GvHD)-free relapse-free survival (GRFS).

Read more on the use of transplantation for the treatment of AML here.

Study design[2]

- Retrospective analysis from data obtained by the EBMT registry (2006-2018)
- Adult patients > 18 years with intermediate or poor risk AML, who had received matched sibling donor or unrelated donor allo-SCT and are in CR1
- Dosing of reduced-intensity conditioning regimens:
  - Bu/Flu (N= 350): intravenous Bu at a total dose 9.6mg/kg for three days plus Flu
  - TBI/Flu (N= 168): TBI at a total dose of 8Gy plus Flu
- Patient and transplantation characteristics are shown in **Table 1**

Table 1. Patient and transplantation characteristics[2]

	Bu/Flu (N= 350)	**TBI/Flu (N= 168)**	**p value**
Median follow-up, months	23	57	**< 0.0001**
Age, years	56.5 (18-73)	50 (20.5-71)	**< 0.0001**
Interval: diagnosis to allo-SCT, months	5 (1-18)	4 (2-16)	**< 0.0001**
Male patients, %	53	58	0.33
Poor risk AML karyotype, %	26	26	0.96
Karnofsky score < 80, %	4	0	**0.004**
Donor, %:			**0.02**
Matched sibling	47	58	
Unrelated	53	42	
Stem cell source, %			0.07
Bone marrow	9	5	
Peripheral blood	91	95	

allo-SCT, allogeneic stem cell transplantation; BU, busulfan; Flu, fludarabine; TBI, total body irradiation
Statistically significant values are indicated in bold

Key findings[2]

- Engraftment rate was 99% for both regimens
- In the total patient cohort, univariate analysis revealed that:
  - RI was significantly higher in the Bu/Flu group than those receiving TBI/Flu (p= 0.01)
  - NRM (p= 0.18) and LFS (p= 0.15) were not significantly different between the two conditioning regimens

- Acute GvHD (aGvHD) of grade 3-4 was the only significant GvHD-related difference between the two conditioning regimens. This was observed when stratifying patients by age. In patients < 50 years old grade 3-4 aGvHD was significantly lower with TBI/Flu than Bu/Flu (**Table 2**)

Table 2. Univariate analysis for GvHD incidence by age group

TBI/Flu *vs* Bu/Flu	**Patients < 50 years**	**Patients ≥ 50 years**
aGvHD grade 2-4, %	15 *vs* 26 (p= 0.12)	23 *vs* 24 (p= 0.74)
aGvHD grade 3-4, %	**2 *vs* 12 (p= 0.02)**	5 *vs* 8 (p= 0.37)
cGvHD overall, %	38 *vs* 38 (p= 0.91)	37 *vs* 37 (p= 0.92)
cGvHD extensive, %	20 *vs* 10 (p= 0.08)	16 *vs* 17 (p= 0.8)

aGvHD, Acute GvHD; BU; busulfan; cGvHD; Chronic GvHD; TBI, total body irradiation
Statistically significant values are indicated in bold

- When comparing patients < 50 years of age with those ³ 50 years, Cox modelling revealed that **(Table 3):**
  - In patients < 50 years of age, RI, LFS, OS, GRFS and incidence of aGvHD grade 3-4 were significantly improved with TBI/Flu compared to Bu/Flu
  - In patients ≥ 50 years only NRM was significantly higher with TBI/Flu *vs* Bu/Flu

Table 3. Cox modelling of outcome parameters by age group

TBI/Flu *vs* Bu/Flu	**Patients < 50 years**			**Patients ≥ 50 years**		
	HR	**95% CI**	**p value**	**HR**	**95% CI**	**p value**
RI	**0.49**	**0.24-1.0**	**0.049**	0.64	0.33-1.28	0.21
NRM	0.17	0.02-1.39	0.1	**3.98**	**1.81-8.76**	**0.0006**

LFS	**0.45**	**0.23-0.88**	**0.02**	1.31	0.80-2.12	0.28
OS	**0.29**	**0.13-0.63**	**0.002**	1.53	0.92-2.55	0.1
GRFS	**0.53**	**0.31-0.92**	**0.02**	1.09	0.71-1.68	0.69

Bu, busulfan; Flu, fludarabine; GRFS, graft-versus-host disease (GvHD)-free, relapse-free survival; LFS, leukemia-free survival; NRM, non-relapse mortality; OS, Overall survival; RI, relapse incidence; TBI, total body irradiation
Statistically significant values are indicated in bold

Conclusion

Both the reduced-intensity conditioning regimens examined in this retrospective study (TBI/Flu and Bu/Flu) resulted in low RI rates and low NRM following allo-SCT. Thus, they both present a good regimen for patients with AML in CR1. When looking at the patient population in two different age groups (< 50 or ≥ 50 years old), TBI/Flu was more efficacious than Bu/Flu in younger patients with a lower RI and higher GFRS, LFS, and OS. The incidence of acute grade 3-4 GvHD was also significantly reduced with TBI/Flu *vs* Bu/Flu in younger patients. Nevertheless, in older patients (≥ 50 years old) TBI/Flu was associated with an increased NRM risk and should be used with caution. Despite the limitation of the retrospective design of this study, the results are very informative and encourage further prospective clinical trials with age-dependent stratification of patients to such conditioning regimens.

References

1. AML Global Portal. Monthly editorial theme | An introduction to the use of transplantation for the treatment of AML. 2019 Nov 11. URL: https://amlglobalportal.com/medical-information/monthly-editorial-theme-an-introduction-to-the-use-of-transplantation-for-the-treatment-of-aml. Published; November 11 2019, [Accessed on Dec 27, 2019]
2. Giebel S. *et al.,* Reduced risk of relapse for total body irradiation + fludarabine compared to busulphan + fludarabine as “reduced-toxicity” conditioning for patients with acute myeloid leukemia treated with allohsct in first complete remission. a study by the Acute Leukemia Working Party of the EBMT; 2019 Dec 09. Oral abstract #255: 61st American Society of Hematology Annual Meeting & Exposition, Orlando, FL