Long-term follow-up of allogeneic stem cell transplantation in relapsed/refractory Hodgkin lymphoma

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High-dose chemotherapy and autologous hematopoetic cell transplantation can rescue no more than 50% of patients with relapsed/refractory (RR) Hodgkin lymphoma (HL).[1,2] The novel anti-CD30 brentuximab vedotin (BV), the anti-PD1 nivolumab or pembrolizumab, and allogeneic (allo)-HCT represent treatment options in this subset. Importantly, the 2015 European and American guidelines recommend reduced-intensity conditioning allo-HCT for eligible patients relapsed after an autologous hematopoetic cell transplantation.[3,4]

We present a long-term follow-up analysis on 69 consecutive RR HL patients treated with allo-HCT, between May 2000 and December 2015, at three Transplant Centers in Northwest Italy (AOU Città della Salute e della Scienza of Torino, AO Santa Croce e Carle of Cuneo, and AO Santi Antonio, Biagio e Cesare Arrigo of Alessandria).

Patient, disease and transplant characteristics are summarized in Table 1. Patients received a median of 4 therapy lines (range, 2–6) before allo-HCT. Forty patients (58%) received an autologous hematopoietic cell transplant 7.6 months (range, 1.6–48.2) before allo-HCT; 24 patients (35%) underwent a programmed tandem auto/allo-HCT. Primary graft failure[5] occurred in 1 patient (1.5%) receiving PBSC from an unrelated donor.

Median overall survival (OS) from diagnosis was 10.9 years (range, 1.18–18.6+). After a median follow-up in survivors of 7.2 years (range, 0.1–13.8+) from allo-HCT, 5-year OS and relapse-free survival (RFS) were 51.4% and 38.9%, respectively (Figures 1a and b). Five-year RFS was 45.9% and 12.5% in responsive (CR+PR) and non-responsive (others) patient cohorts, respectively, (P = 0.008) (Figure 1e). RFS of patients in CR at the time of allo-HCT (n = 29) compared with patients in PR (n = 23) did not significantly differ (hazard ratio = 1.71, 95% confidence interval (CI) 0.78–3.72, P = 0.18). There was a trend for better 5-year OS in responsive patients as compared with non-responsive, 54.6% vs 37.5% (P = 0.19). We observed also a trend to better OS in patients who developed chronic GvHD compared with patients who did not (hazard ratio = 0.65, 95% CI 0.29–1.48, P = 0.3 (57 evaluable patients)).

Overall, 32 patients died mainly because of disease recurrence (n = 20). The higher risk of failure in terms of RFS of non-responsive patients was confirmed by univariate Cox regression (hazard ratio = 2.34, 95% CI 1.22–4.50, P = 0.011). Cumulative incidence of non-relapse mortality (NRM) was 17.7% at 5 years (Figure 1c). Causes of NRM were hemorrhagic alveolitis (n = 2), infections (N = 5) and GvHD (N = 5). Patients younger than 35 years old had a

Table 1. Patient and disease characteristics

Characteristics	*Overall*
Patients, *n*	69
Male/female, *n* (%)	33 (48)/36 (52)
Median age at allo-HCT, years (range)	34 (18–64)
Disease status at allo-HCT	
CR, *n* (%)	29 (42)
PR, *n* (%)	23 (33)
Other, *n* (%)	16 (23)
Not evaluable, *n* (%)	1 (1)
Stage	
I–II, *n* (%)	32 (46)
III–IV, *n* (%)	36 (52)
Not evaluable, *n* (%)	1 (1)
Therapy lines	
⩽3, *n* (%)	32 (46)
⩾4, *n* (%)	37 (54)
Previous auto-HCT	64 (93)
Immunosuppression	
CNI/MTX	53 (77)
CNI/MMF	12 (17)
CNI/CY/MMF	2 (3)
CNI/alemtuzumab	2 (3)
ATG	
Yes, *n* (%)	35 (51)
No, *n* (%)	34 (49)
Conditioning intensity	
RIC or non-myeloabative	64 (93)
MAC	5 (7)
Donors	
HLA-matched family members, *n* (%)[a]	28 (41)
HLA-haploidentical, *n* (%)	2 (3)
HLA-matched unrelated, *n* (%)	38 (55)
Cord, *n* (%)	1 (1)
Source of stem cells	
Peripheral blood, *n* (%)	61 (88)
Marrow, *n* (%)	7 (10)
Cord, *n* (%)	1 (1)
Brentuximab vedotin	
Pre-allo-HCT, *n* (%)	12 (17)
Post-allo-HCT, *n* (%)	6 (9)
No, *n* (%)	49 (71)
Not evaluable, *n* (%)	1 (1)

Abbreviations: ATG = anti-thymocyte globulin; CNI = calcineurin inhibitors; CY = cyclophosphamide; HCT = hematopoietic cell transplant; MAC = myeloablative conditioning; MMF = mycophenolate mofetil; MTX = methotrexate; RIC = reduced-intensity conditioning. [a]One patient was one Ag HLA-mismatched.

lower NRM than older patients (8.7% vs 27.1%, $P = 0.051$). NRM did not differ between responsive and non-responsive patients (SDHR 1.08, 95% CI 0.30–3.96, $P = 0.9$).

Cumulative incidence of grade II–IV acute GvHD was 36.7% (60 evaluable patients). At follow-up, cumulative incidence of all grades of chronic GvHD was 45.6% (57 evaluable patients) (Figure 1d). Of note, six additional patients developed chronic GvHD after disease relapse likely due to rapid immunosuppression taper or subsequent donor lymphocyte infusion (DLI).

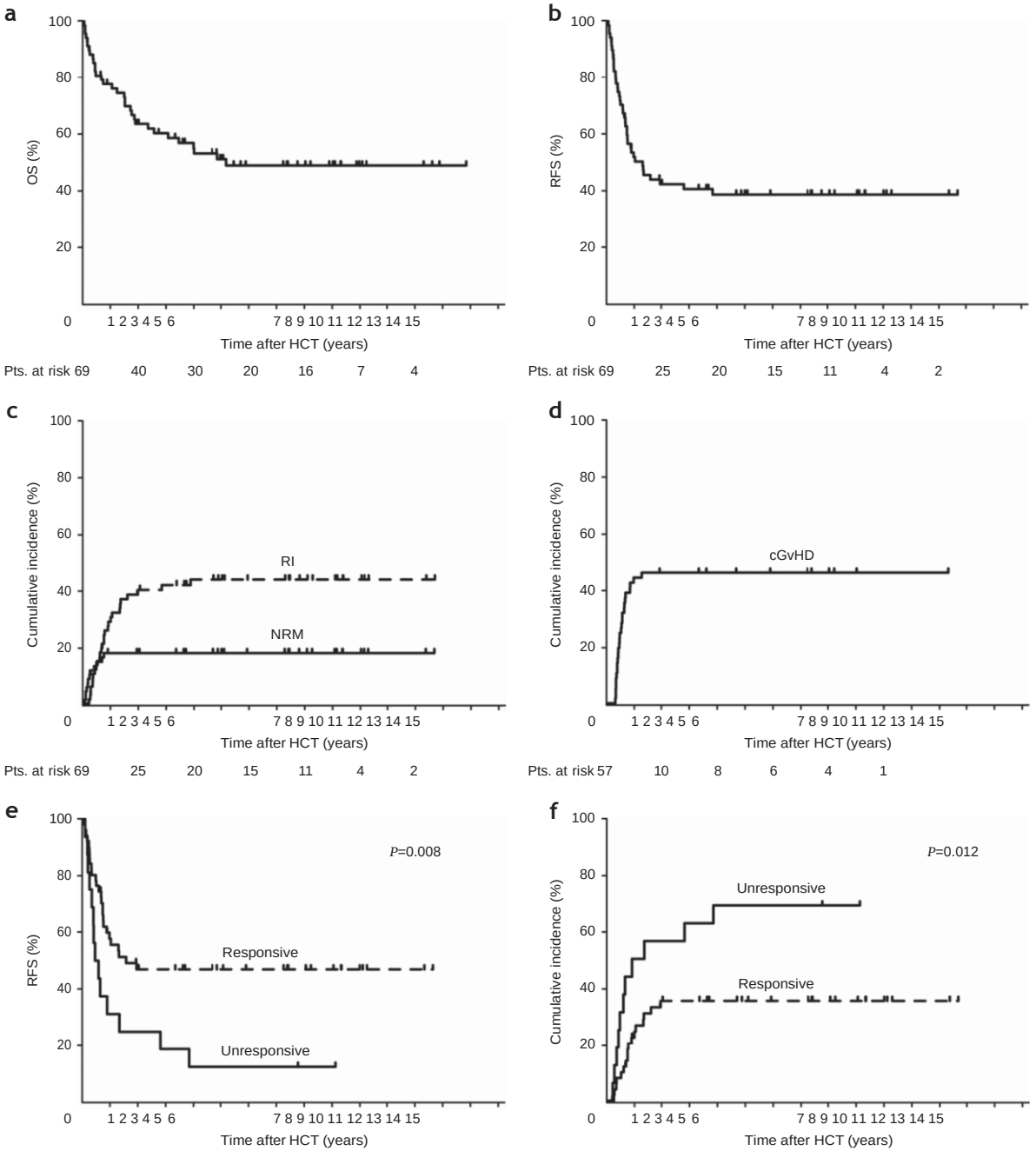

Figure 1. Kaplan–Meier curves of overall survival (a) and relapse-free survival (b); cumulative incidence curves of relapse, non-relapse mortality (c) and cGvHD (d). Kaplan–Meier curves of relapse-free survival (e), and cumulative incidence curves of relapse (f) for patients at least in PR at allo-HCT (responsive) and for patients with active disease (unresponsive). cGvHD, chronic GvHD; RI, relapse incidence.

Overall, 1-, 3- and 5-year relapse incidence was 31.8%, 41.4% and 43.4%, respectively (Figure 1c). Median time to relapse was 7.8 months (range, 1.8–45.5). Twenty-one/28 (75%) relapses occurred within 1 year from allo-HCT. Patients with non-responsive disease had a significantly higher relapse incidence than responsive patients, 68.7% vs 35.3% ($P = 0.012$) (Figure 1f). The negative impact of active disease at allo-HCT was confirmed by univariate competing-risk regression (SDHR 2.65, 95% CI 1.26–5.51, $P = 0.001$).

Among 28 relapsed patients, 13 (46%) received DLI alone ($n = 3$), with brentuximab ($n = 3$) or with chemotherapy ($n = 7$) after a median of 18.7 months (range, 3.4–50) from allo-HCT.

The remaining 15 patients received chemotherapy alone or best supportive care. DLI were from unrelated ($n = 4$), matched-related siblings ($n = 8$) and HLA-haploidentical ($n = 1$) donors. Median number of DLI received per patient was 2 (range, 1–7) and the median number of $CD3^+$ lymphocytes infused was 1×10^7 $CD3^+$ cells/kg (range, 1×10^6–1×10^8). Four patients achieved CR, five PR and four were unresponsive. The median time to next treatment was 11 months (range, 3–123). Post-DLI GvHD occurred in four patients, and two of them required immunosuppression. Patients who received DLI had a median OS from the time of first relapse of 4.5 years (range, 1.2–12.2+). At last follow-up, 8 out of 28 relapsed patients (29%) were alive. Of those, six had received DLI.

Since 2011, BV was used at the conventional dose (1.8 mg/kg IV once every 3 weeks) in 18 patients. Twelve patients (67%) received BV as bridge to allo-HCT for a median of six cycles (range, 3–13). The median time between the last BV cycle and allo-HCT was 1.7 months (range, 0.3–4). Only three patients failed to achieve at least PR, with an overall response rate of 75%. BV was also administered as salvage for post-allo-HCT relapse in 6 patients (median 11 cycles, range, 7–16), 3 of whom did not respond to prior DLI. Two additional patients received DLI after BV. The first BV cycle was administered after a median of 6 months from allo-HCT (range, 2.6–16.7). Five patients achieved CR and 1 patient PR, with a median survival from the first BV cycle of 27.2 months (range, 10.5–55.5+). Four of 6 patients were alive at last contact. None of the patients treated with BV had unexpected toxicity or GvHD flare. One patient developed grade I hematological and neurological toxicity, which did not require drug discontinuation, and another experienced grade II gastrointestinal toxicity.

Our report combines a 15-year experience of allo-HCT for RR HL in three Italian Transplant Centers after a remarkable median follow-up longer than 7 years. Given the long study period, transplant preparative regimens and GvHD prophylaxis changed over time. Overall, all but five of our patients received reduced-intensity conditioning regimens, given that myeloablative conditionings were commonly associated with worse outcomes in HL patients.[6–8] However, a recent study on 312 patients comparing reduced-intensity conditioning and myeloablative allo-HCT hinted at a better disease control with the latter due to recent decrease in NRM.[9]

Other recent studies evaluated the impact of donor type on clinical outcomes for HD patients.[10,11] Overall, whether a haploidentical donor should be preferred to an unrelated donor, especially when HLA mismatches are present, remains a matter of debate. In our study, clinical outcomes between related and unrelated donor HCT did not differ.

Overall, the main cause of treatment failure was relapse. Of note, most relapses (75%) occurred within 1 year from allo-HCT. In several studies, chronic GvHD appeared to confer protection against disease recurrence.[12,13] We observed only a trend toward a decreased relapse incidence in patients with chronic GvHD. The therapeutic potential of a graft-versus-lymphoma effect in our series is suggested by the long-term survival of patients after DLI. The efficacy of DLI in HL was previously described by Peggs *et al.*[14] in patients who underwent *in vivo* T-cell depleted allo-HCT. Nineteen of 24 relapsed patients (79%) responded to DLI (14 CRs, 5 PRs), with a 4-year OS from relapse of 59%.

Given the poor prognostic features of patients included in this study, the 5-year OS higher than 50% is highly encouraging, and similar to those reported by the EBMT consortium[15] on 92 HL patients with 4 years of follow-up and 4-year OS of 41%. Importantly, our long follow-up allowed to observe that both OS and RFS curves reached a plateau after around 5 years, which confirmed the curative potential of allo-HCT in RR HL. Several studies showed the dismal outcome of patients with active disease at the time of allo-HCT.[7,12–14] In our report, the presence of responsive disease was the only statistically significant predictor of lower relapse incidence and better RFS. However, we only observed a trend toward better OS between responsive and non-responsive patients. This may be due to long-term responses in relapsed patients where a prolonged and persistent graft-versus-lymphoma effect may have played a pivotal role.

Evidence of very high response rates obtained with novel agents are emerging in RR HL. However, response duration after BV in early phase trials was in the order of 10 months only and follow-up after anti-PD1s is too short to draw conclusions.[16–19] Several other groups reported promising results with BV prior to allo-HCT, or as salvage for post-allo-HCT relapse.[20–22] In our experience, the use of BV did not add unexpected toxicity and showed efficacy on disease reduction before allo-HCT. This is of particular interest, given that disease status at allo-HCT was the only predictor of RFS. Furthermore, BV played a role, alone or in association with DLI, for the treatment of post-transplant disease recurrence.[23]

In conclusion, our study showed that allo-HCT is feasible and effective in RR HL. The plateau of survival curves was more than likely due to a prolonged and persistent graft-versus-lymphoma effect. BV was safe and effective as a bridge to allo-HCT in the majority of treated patients and as rescue in post-allo-HCT relapse. A combination strategy of allo-HCT with BV and/or other novel agents may further improve clinical outcomes of cell therapies in HL and should be evaluated in prospective trials.

CONFLICT OF INTEREST

BB has received honoraria from Gilead, Pfizer, Celgene, Hospira and research support from Celgene, Pierre Fabre, ADIENNE, Hospira Italia, MSD Italia. MB has received research support, consultancy and scientific advisory board from Celgene and Janssen-Cilag. The remaining authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

LG, MF, FZ, NM and BB designed the study. LG, MF and BB wrote the report. NM, MP, AB and BB supervised the clinical conduction of the study and data analysis. LG, MF, RS, NM, FZ and MP supervised data collection, analyzed data, and reviewed and assisted in writing the manuscript. LG, MF, FZ, RS, LB, EM, CD, GI, SA, MB, UV, NM, MP, AB and BB recruited the patients. RP did the statistical analysis.

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