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Long term follow-up of BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation in relapsed advanced stage follicular lymphoma

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ABSTRACT

This is an analysis in 171 patients comparing BEAM-Auto and BEAM-Allo (alemtuzumab)-hematopoietic stem cell transplantation in relapsed follicular lymphoma. BEAM-Allo group had a lower 10 years cumulative incidence of relapse(31.4% vs 55.1%, $p = 0.042$), a trend to a plateau in survival but no statistical differences in OS or DFS, and a TRM of 24%. When transplanted in CR BEAM-Allo patients had better OS and DFS. Incidence of acute and chronic GVHD was 16.6% and 22%. 29% of BEAM-Allo patients received DLI (all but two remain in CR and alive). Our data supports Allo-HSCT as a potential curative treatment for selected patients with FL.

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1. Introduction

Follicular lymphoma (FL) accounts for about 20% of all non-Hodgkin lymphomas, with a median age at diagnosis of 60 years [1–3]. Despite several advances in its management, it remains an incurable disease with a historical median survival ranged from 8 to 10 years, characterised by recurrent relapses with no consensus on the therapeutic sequencing. The addition of anti-CD20 moAb Rituximab to standard chemotherapy as well as maintenance has improved the response rate and also the survival of the disease [4–10]. The new radio-immunoconjugates have also improved the response rates (60–70%) in relapsed disease [11,12].

Hematopoietic stem cell transplantation (HSCT) has been shown to be an option for relapsed and refractory patients with chemosensitive disease but has not shown any advantage as first line treatment [13–15]. Autologous HSCT (Auto-HSCT) has shown OS and PFS rates of 70% and 50% in relapsed disease, with TRM of 7%. However, relapse rate remains around 50%, with continuous relapse pattern even years after transplant [16,17]. Post autograft maintenance with Rituximab has recently showed an improvement in PFS, but not in OS [18]. Allogeneic HSCT (Allo-HSCT) is the only known curative option for FL patients, with a lower relapse rate compared to Auto-HSCT, probably due to the existence of a graft versus lymphoma (GVL) effect [19,20]. Myeloablative conditioning regimens showed durable remissions (5 yr OS and EFS: 52–85% and 43–75%) [21,22]. The higher TRM of 30–38% when compared to Auto-HSCT has been the main limitation to patients proceeding [19,20].

The development of reduced intensity conditioning (RIC) regimens has lowered the TRM while maintaining the GVL effect, making allogeneic HSCT applicable to patients previously ineligible. Studies have shown 3–5 years OS and EFS ranging from 52 to 81% and 43 to 75% [23–26], with a graft versus host disease (GVHD) rate of 40%, which remains one of the most important complications and contributing factors for morbidity/mortality [23,27,28]. T-cell depleted regimens, with in-vivo addition of alemtuzumab incorporated into the conditioning regimen have shown comparable outcomes with OS ranging from 67 to 76%, relapse rate of 20–26%, with a lower rate of GVHD ranging from 18 to 20% [25] and a lower NRM ranging from 15 to 22%. The use of donor lymphocyte infusion (DLI) for mixed chimerism and to re-induce remissions in patients who relapse after Allo-HSCT has also supported the potential curative option of allogeneic stem cell transplantation based on the induced GVL effect [25].

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We previously reported our data comparing BEAM-Auto and BEAM-Allo (alemtuzumab) HSCT in relapsed FL showing a lower relapse rate in the allograft setting, but no differences in OS or DFS [29]. An update of this analysis is presented in this study with a median follow-up of 7.7 years in the BEAM-Allo and 5.5 years in the BEAM-Auto groups.

2. Design and methods

2.1. Patients

One hundred and seventy one consecutive patients with diagnosis of FL who received a BEAM-autologous HSCT (BEAM-Auto; $n = 117$) or BEAM-alemtuzumab HSCT (BEAM-Allo; $n = 54$) between 1992 and 2010 were retrospectively analysed from 2 different UK centres. FL was diagnosed according to the WHO classification. Indications for BEAM-Alemtuzumab HSCT included chemosensitive disease following salvage treatment, donor availability of at least a 9 out of 10 HLA match (sibling SIB or volunteer unrelated VUD) or failed CD34 stem cell mobilisation. Patients underwent BEAM-Auto HSCT according to patient' choice, no donor availability or physician decision. The transplant protocol was ethically approved by local committee and all the patients gave written consent before entering the study.

Patients characteristics in the whole cohort, are summarised in Table 1. The BEAM-Auto group was older with a median age of 57 years (range 27–69) compared to BEAM-Allo with 48 years (range 30–63) ($p = 0.000$). No differences were found in the duration of last remission between two groups or the number of chemotherapy lines prior to transplant. 74% of patients (40/54) in the BEAM-Allo group received Rituximab prior to transplant compared to 61.5% (72/117) in the BEAM-Auto ($p = 0.109$). None of the patients had a previous autograft in the BEAM-Auto group, while three patients had one previous autograft in the BEAM-Allo group. There was no difference in the disease status at the time of transplant between the two groups in terms of complete remission (CR), partial remission (PR) or progressive disease (PD). A statistically higher proportion of high grade transformation (HGT) was noted in the BEAM-Auto (48.3% vs 28.3%, $p = 0.015$). The CD34+ cell dose infused was similar between the two groups, with a median of 5.0×10^6 CD34/kg (range 1.47–17.28) in the BEAM-Allo compared to 5.2×10^6 CD34/kg (0.62–25.8) in BEAM-Auto group ($p = 0.308$). The progenitor source used was mainly peripheral blood, 89% in BEAM-Allo compared to 94% in BEAM-Auto. The BEAM-Allo group had 67% sibling donors, and of the VUD 87% were 10/10 matched.

2.2. CD34+ mobilisation, conditioning regimen, supportive care and monitoring

Cyclophosphamide 1.5 g or 3 g/m^2 plus G-CSF 5 μg/kg for 5 days was used as CD34+ stem cell mobilisation regimen in the Auto-HSCT, and G-CSF 10 μg/kg for 4 days was given for donors in the allogeneic setting (if peripheral blood transplant). Conditioning was BCNU carmustine 300 mg/m^2 day-6, cytarabine 200 mg/m^2 twice daily day-5 to day-2, etoposide 200 mg/m^2 day-5 to day-2 and melphalan 140 mg/m^2 day-1. Recipients of allogeneic stem cells received Alemtuzumab (Campath 1-H) 10 mg/d or 20 mg/d (Nottingham and King's College Hospital respectively) day-5 to day-1. Ciclosporin (1.5 mg/kg i.v.) was used for GVHD prophylaxis from day-1, and tapered from day +56 in the absence of GVHD.

Patients received antimicrobial and antifungal prophylaxis and acyclovir. CMV reactivation was monitored by antigenemia and more recently by PCR. Granulocyte colony-stimulating factor was administered from day +7 post transplant.

Disease status was monitored at day +100 after transplant with computed tomography (CT) and bone marrow analysis. Chimerism analysis was performed by short tandem repeat (STR) PCR after BEAM-alemtuzumab HSCT in bone marrow and peripheral blood (unfractionated blood-UF, CD3+ and CD15+ isolated cells) at days +26, +56, +100, 6 months and then annually or earlier if clinically indicated. Mixed chimerism was defined as more than 1% of recipient in UF and 5% in CD3+ or CD15+. Indications for DLI after day 100 were falling chimerism in two consecutive measures and stable mixed chimerism (both situations in absence of GVHD) or relapse disease in combination with chemotherapy. Acute and chronic GVHD were assessed and graded according to NIH published consensus criteria [30,31].

Table 1
Patient and transplant characteristics, BEAM-autograft and BEAM-alemtuzumab Allo-HSCT.

		Total	BEAM-Auto	BEAM-Allo
Follow up	Median (years)	6.5	5.5	7.7
	Range	0.8–18.2	0.2–18.2	2.14–14.2
	n	171	117	54
Age	Median (years)	54	57	48
	Range	27–69	27–69	30–63
>60 years	*n* (%)	46 (27)	44 (38)	2 (4)
Date of transplant	1992–1999	30 (18)	27 (23)	5 (9)
	2000–2010	141 (82)	90 (77)	49 (91)
Disease status at HSCT	Complete remission	52 (30)	38 (33)	14 (26)
	Partial remission	107 (62)	70 (60)	37 (69)
	Progressive disease	8 (5)	5 (5)	3 (5)
Duration of last remission	<1 year	43 (25)	30 (26)	13 (24)
	1–2 years	37 (22)	23 (20)	14 (26)
	>2 years	90 (53)	63 (54)	27(50)
High grade transformation	Yes	71 (41)	56 (48)	15 (28)
Previous Rituximab use	Yes	112 (65)	72 (61)	40 (74)
Previous HSCT	Yes	2 (1)	0	2 (4)
Prior chemo/radiotherapy	Median lines	2 (1–11)	2 (1–7)	3 (1–11)
>3 chemotherapy lines	*n* (%)	85 (50)	53 (45)	32 (59)
Donor sex	Male			34 (63)
	Female			19 (36)
Source of stem cells	PBSC	158 (93)	110 (95)	48 (89)
	Bone marrow	12 (7)	6 (5)	6 (11)
CD34+ dose ($\times 10^6$ kg^{-1})	Mean	5.12	5.92	5
	Range	0.7–17.3	0.7–25.8	1.5–17.3

Patients and transplant characteristics in total population, BEAM-autologous and BEAM-alemtuzumab allogeneic stem cell transplantation.

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