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Use of brentuximab vedotin as salvage therapy pre-allogeneic stem cell transplantation in relapsed/refractory CD30 positive lympho-proliferative disorders: a single centre experience

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Key words
Hodgkin lymphoma, anaplastic large cell lymphoma, allogeneic stem cell transplantation.

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Abstract

Background: The role of brentuximab peri-allogeneic transplantation in patients with relapsed and/or refractory CD30 positive lymphomas remains poorly defined.
Aim: To assess the outcome of use of brentuximab as a bridge to allogeneic stem cell transplantation (SCT) in patient with relapsed/refractory CD30+ classic Hodgkin lymphoma cHL and anaplastic large cell lymphoma (ALCL).
Methods: Outcomes of consecutive patients with relapsed/refractory cHL/ALCL treated with brentuximab as a bridge to SCT were determined by retrospective review of individual medical records. Survival analysis was measured from start of brentuximab treatment.
Results: A total of 12 patients (10 cHL, 2 ALCL) had received brentuximab as a planned bridge to allogeneic SCT. Median age was 27 years (range 20–54 years); median prior lines of therapy was 4 (range 3–6) and all except one patient had undergone prior autologous SCT (92%). Patients received at median of 3 brentuximab doses pre-allogeneic SCT (range 1–4), with an overall response rate of 66.7%. At a median follow up of 30 months (range 6–52 months), 2 years progression free survival and overall survival post-allogeneic SCT is 58 and 92% respectively. Incidence of non-relapse mortality, grade 3–4 acute graft versus host disease and extensive stage chronic graft versus host disease is 8, 17 and 18% respectively. Of five patients who subsequently relapsed post-SCT, four remain alive with disease control post manipulation of immune-suppression.
Conclusion: Our experience suggests that brentuximab use pre-allogeneic SCT is not associated with any significant post-transplant toxicity, and is associated with a rapid response in a majority of patients with relapsed/refractory CD30 positive lymphomas. Brentuximab may thus provide a non-toxic bridge to allogeneic SCT for patients with relapsed/refractory CD30 positive cHL or ALCL.

Introduction

Treatment of patients with relapsed and/or refractory CD30 positive lymphomas, including classic Hodgkin lymphoma (cHL) and anaplastic large cell lymphoma (ALCL), remains challenging. Conventional salvage chemotherapy followed by autologous stem cell transplantation (ASCT) has been associated with long-term remission rates in only a relative minority of patients,[1,2] with similar medium term overall and disease free survival outcomes reported for those undertaking allogeneic transplantation.[1,3,4]

Brentuximab vedotin is an anti-CD30 antibody conjugated by a protease-cleavable linker to a microtubule disrupting agent, monomethyl auristatin E. Brentuximab vedotin has established efficacy in treatment of relapsed/refractory cHL and ALCL,[5] with associated high response rates and limited toxicity.[6,7] Based on this published efficacy, we developed a clinical pathway incorporating brentuximab vedotin as bridging therapy pre-allogeneic stem cell transplantation (SCT) for patients with relapsed/refractory CD30 positive cHL and ALCL at our institution. Herein we report the outcome of the first 12 patients treated with brentuximab pre-allogeneic transplantation, and

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highlight the minimal toxicity and potentially enhanced post-transplant outcomes experienced with this approach.

Methods

To access brentuximab vedotin as bridging therapy pre-transplantation all patients were required to meet the following three selection criteria: (i) biopsy proven CD30 positive cHL or ALCL; (ii) relapsed disease following prior ASCT, or disease not considered suitable for ASCT and (iii) refractory disease (i.e. not achieving at least partial response) to most recent line of salvage chemotherapy. Patients who suffered relapse post a prior allograft were excluded. Brentuximab vedotin dosing schedule was 1.8 mg/kg IV q21 days for a maximum of four doses. Routine response assessment to brentuximab was planned post cycle 3 of therapy through positron emission tomography/computed tomography (PET/CT) scan using the International Working Group revised response criteria for malignant lymphoma;[8] further response assessment was routinely performed approximately day 100 post-transplantation.

Patients were identified from an institutional database and outcomes determined retrospectively from medical records. The National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03 was used to evaluate toxicity.

Conditioning protocols for allogeneic transplantation included both reduced intensity (fludarabine 125 mg/m^2 plus melphalan 120 mg/m^2) and myeloablative conditioning regimens (cyclophosphamide 120 mg/kg and TBI 12Gy). Stem cell source was G-CSF stimulated peripheral blood progenitor cells in all cases; all grafts were T-cell replete. Graft versus host disease (GVHD) prophylaxis consisted of cyclosporine 3 mg/kg/day and day 1, 3, 6 and 11 methotrexate.

Survival analysis was calculated from both start of brentuximab vedotin treatment and SCT to progression,

Table 1 Baseline characteristics

	cHL	ALCL
Number	10	2
Median age (range) (years)	29 (20–54)	26 (24–27)
Sex (M/F)	7/3	2/0
Diagnostic stage		
1A/1B	1/0	—
2A/2B	3/1	—
3A/3B	0/4	1/0
4A/4B	0/1	0/1
Median prior lines of therapy (range)	4 (3–6)	3 (3–3)
Prior IFRT	10	2
Prior autologous SCT	9	2
Median time (months) from initial diagnosis to commencing brentuximab (range)	41 (19–60)	28 (13–42)
Median no. brentuximab doses pre-allograft (range)	3 (3–4)	2 (1–3)
Response to brentuximab		
CR	3	1
PR	4	0
SD	3	1†
PD	0	0
Allograft conditioning regimen		
Flu/Mel	10	1
Cy/TBI	0	1
Donor type		
Matched sibling donor	1	1
Matched unrelated donor	9	1
Sex matched	7	1
Sex mismatched	3	1

†SD assessed clinically only. ALCL, anaplastic large cell lymphoma; cHL, classic Hodgkin lymphoma; CR, complete remissions; IFRT, involved field radiotherapy; PD, progressive disease; PR, partial remission; SCT, stem cell transplantation; SD, stable disease.

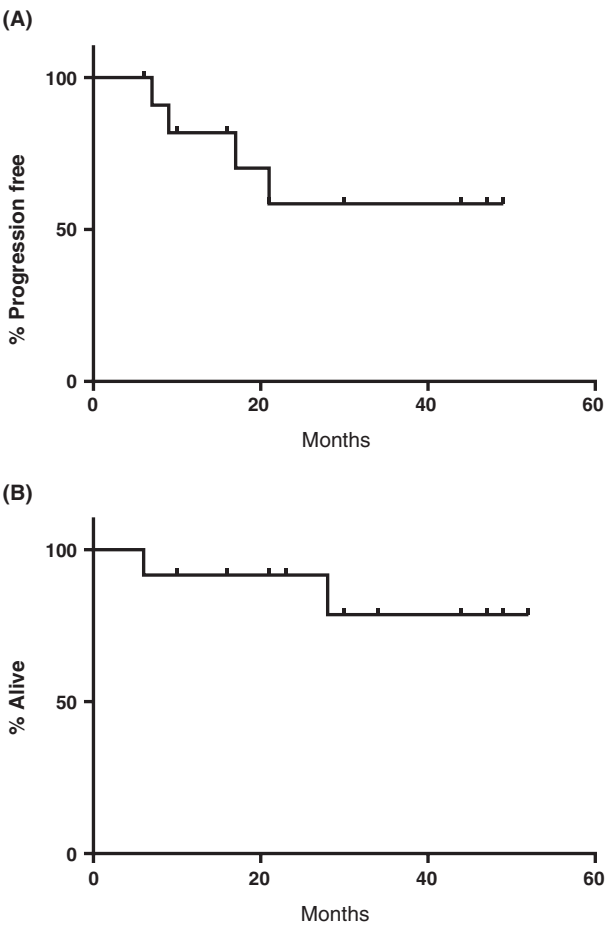

Figure 1 (A) Progression free survival (PFS) from start of brentuximab all patients; (B) overall survival (OS) from start of brentuximab all patients.

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relapse or last follow up for progression free survival (PFS), and to death or last follow up for overall survival (OS) respectively. Survival analysis was done using the Kaplan–Meier method. Non-relapse mortality (NRM) was defined as any non-lymphoma related death post commencement of brentuximab. GVHD was assessed and graded as per Seattle criteria.[9,10]

Results

Between July 2011 and December 2015, a total of 12 patients with relapsed/refractory cHL or ALCL received brentuximab vedotin as a bridge to allogeneic transplantation. Baseline characteristics are shown in Table 1. For the whole cohort, median age at time of commencing brentuximab was 27 years (range 20–54 years), median number of prior lines of therapy was 4 (range 3–6) and all except one patient had undergone prior autologous transplantation (92%). All patients had been previously treated with involved field radiotherapy (IFRT), and a majority of patients suffered advanced stage disease at initial diagnosis. Median time from initial diagnosis to commencing brentuximab therapy was 41 months (range 13–60 months).

A majority of patients (n = 9) underwent allografting post undertaking response assessment after brentuximab dose #3; two patients received a fourth dose of brentuximab pre-transplantation due to delays in donor availability and another only one dose of brentuximab due to scheduling issues with TBI – this patient was subsequently transplanted without repeat PET/CT disease assessment, but clinically maintained stable disease post their single brentuximab infusion. Overall disease response to brentuximab was 66.7% (Table 1).

Brentuximab was generally well tolerated with no grade 3 or 4 toxicities noted; a grade 2 allergic reaction occurred in one patient post dose #2, one patient suffered grade 2 alopecia, and grade 2 elevation of transaminases occurred post dose #2 in another.

Transplant details are also shown in Table 1. A majority of patients underwent matched unrelated donor transplantation (83%). Incidence of grade III–IV acute GVHD post-transplantation was 17% and overall incidence of transplant-related mortality 8%. Of 11 patients surviving post day 100, thus far 2 (18%) and 4 (36%) have developed extensive and limited stage chronic GVHD respectively. Overall disease response post-allogeneic transplantation was 75%, with nine complete remissions (CR), two patients suffering progressive disease (PD) and one patient suffering a transplant-related death prior to their day 100 disease reassessment.

At a median follow up of 30 months (range 6–52 months), estimated 2-year PFS and OS from start of brentuximab therapy was 58 and 92% respectively (Fig. 1A,B). When analysed from allogeneic SCT (median follow up 28 months, range 2–48 months), similar PFS and OS outcomes were observed, highlighting the lack of significant toxicity and/or disease progression occurring post-commencing brentuximab pre-SCT (Fig. 2A,B). Furthermore, overall response to brentuximab did not appear to affect significantly post-CT outcomes (Fig. 2C,D).

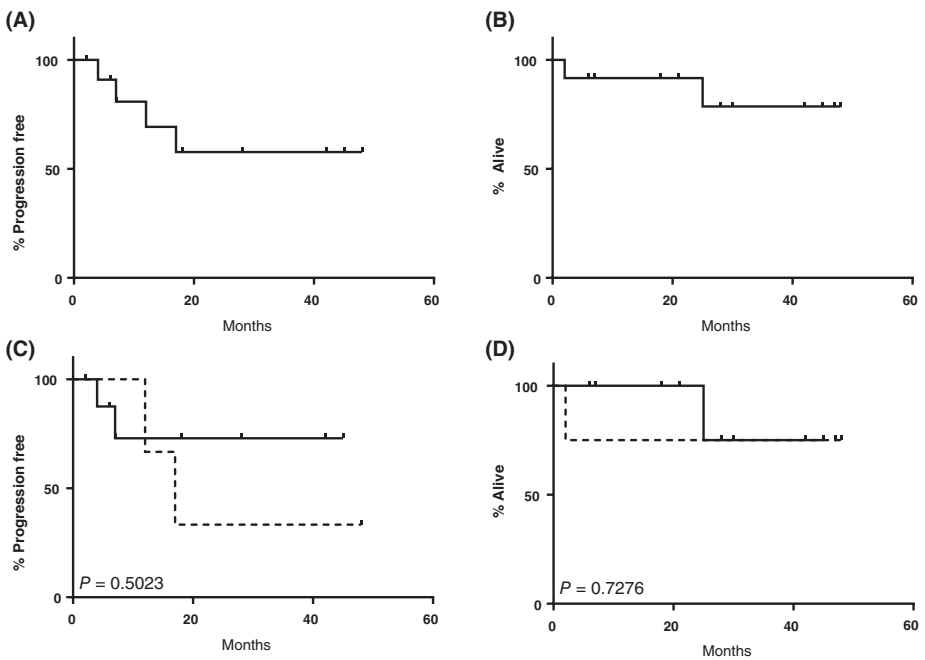

Figure 2 (A) Progression free survival (PFS) from start of stem cell transplantation (SCT) all patients; (B) overall survival (OS) from start of SCT all patients; (C) PFS from transplant based on response to brentuximab; (D) OS from transplant based on response to brentuximab. (–), CR/PR; (··), SD. CR, complete remission; PR, partial remission; SD, stable disease.

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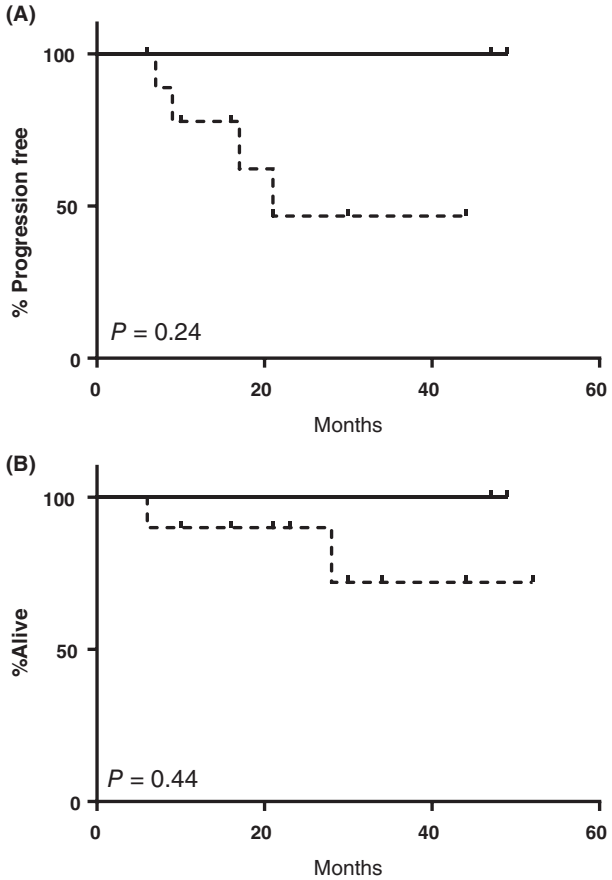

Figure 3 (A) Progression free survival (PFS) from start of brentuximab according to diagnosis; (B) overall survival (OS) from start of brentuximab according to diagnosis. (–), ALCL; (··), HL. ALCL, anaplastic large cell lymphoma; HL, Hodgkin lymphoma.

The outcome of subjects according to diagnosis (HL vs ALCL) is shown in Figure 3. The estimated 2-year PFS and OS for Hodgkin lymphoma patients was 47 and 90%, respectively, with a median PFS of 21 months. Owing to the small number of patients, a statistically significant difference in outcome between HL and ALCL subjects was not demonstrated.

To date, two deaths have occurred, one related to complications of acute GVHD at approximately two post-transplant and another related to PD at 27 months post-brentuximab. Another four patients (25%) have suffered PD post-transplantation, although all remain alive with disease control post manipulation of immune-suppression.

Discussion

Historically patients with relapsed/refractory CD30 positive lymphomas have relatively poor outcomes, with reported 3–5-year OS of only 30–50%.[1,4] Factors associated with improved outcomes include lack of B symptoms or extra nodal disease at progression, initial CR duration of >12 months (1) younger age (<60 years) and absence of significant comorbidities at transplantation.[11,12] Furthermore, chemosensitive disease prior to transplantation has also been associated with improved PFS and OS.[13]

Despite demonstrated efficiency of allogeneic transplantation in relapsed/refractory CD30 lymphomas, limitations include historically high NRM rates, presumably related to the multiple lines of prior therapies patients have received, including ASCT and/or IFRT, prior to consideration of allogeneic transplantation.[14,15]

Although small, our series included a majority of high-risk patients based upon a majority suffering advanced stage at diagnosis, and all receiving ≥3 lines of prior therapy, including ASCT in 92% and prior IFRT in all patients.

Given the high risk nature of our cohort, our 2-year PFS and OS outcomes of 48 and 92% respectively appear particularly favourable. Rates of acute and chronic GVHD and NRM were also similar to reported rates from other centres.[16] On this basis, use of brentuximab pre-allogeneic SCT did not appear to impact negatively on any post-allograft outcome, and indeed, appeared to be associated with significantly enhanced survival outcomes.

Although published phase 2 trials have studied longer brentuximab dosing schedules, typically up to 16 cycles, the durability of these responses appear relatively short in a relapsed/refractory setting, with reported median response durations of approximately 7 and 13 months in cHL and ALCL respectively.[7,12] As median time to brentuximab response is approximately 12 weeks,[7,17,18] we planned for three doses of brentuximab as bridging therapy pre-transplant, expecting a majority of responses to occur by this time and allowing subsequent transplantation to be undertaken prior to risk of further disease progression.

Recently updated phase 2 data of brentuximab therapy in relapsed/refractory cHL suggest that prolonged PFS may be achieved in approximately 50% of patients achieving CR.[19] However, similar to our experience, only a minority (33%) of patients achieved CR post-brentuximab therapy, and one-third of long-term responders underwent a consolidative allogeneic SCT post-brentuximab response.[19] Whether or not allogeneic SCT should be deferred in patients achieving a CR to brentuximab therapy patient group remains to be determined.[19]

Conclusion

Overall, our experience suggests that brentuximab vedotin provides a rapid response in a majority of patients with

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relapsed/refractory CD30 positive lymphomas, with associated minimal toxicity. Use of brentuximab pre-allogeneic transplantation does not appear to be associated with any significant post-transplant toxicity, and thus may provide a non-toxic bridge to allogeneic SCT for patients with relapsed/refractory CD30 positive cHL or ALCL.

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