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Promising remissions in relapsed refractory classical Hodgkin lymphoma patients requiring multiple salvage regimens before transplantation in the brentuximab vedotin era

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ABSTRACT

Relapsed/refractory classical Hodgkin lymphoma (R/R cHL) patients refractory to first line salvage have poor outcomes. Herein we report the outcome of R/R cHL patients requiring ≥two vs. one line in the era of chemo-immunotherapy. Among 55 R/R cHL patients, 33 (60%) required one, 22 (40%) required ≥two lines. At 2 years, the estimated PFS and OS for patients requiring one vs. ≥two lines was 71.2% (50.1–84.7) vs. 51.9% (27.6–71.6), p= 0.16 and 84.6% (63–94) vs. 84% (58–95), p= 0.88, respectively. Patients requiring ≥two salvage lines prior to HCT can achieve comparable outcomes to those requiring one, possibly due to brentuximab vedotin leading to higher CMR rates.

1. Introduction

Salvage chemotherapy followed by consolidative autologous stem cell transplantation (HCT) is the standard approach for patients with chemo-sensitive relapsed / refractory classical Hodgkin lymphoma (R/R cHL) [1,2]. A number of factors have been found to exhibit a negative prognostic including poor performance status, refractory status post first line therapy, extra-nodal disease and the need for multiple chemotherapy regimens prior to HCT [3]. More recently, the presence of metabolically active disease prior to HCT has emerged as a robust prognostic indicator of worse outcome [4–6].

Commonly used platinum- based first salvage regimens including ICE (ifosfamide, carboplatin, etoposide), ESHAP (etoposide, methylprednisolone, cytarabine, cisplatin), DHAP (cisplatin, cytarabine, dexamethasone), or gemcitabine-based regimens such as IGEV (iforsfamide, gemcitabine, etoposide, vinorelbine) or GDP (gemcitabine, dexamethasone, cisplatin) are expected to result in 60–85% overall response rate (ORR), however, majority of responses are partial responses (PR) in nature [7–10]. There is no ideal salvage regimen and typically the preferred one depends on the transplant center's preferences and experience.

The antibody drug conjugate (ADC) Brentuximab vedotin (Bv) has been used as part of salvage regimens or as post HCT consolidation with improved remission rates [11–15]. Patients with R/R cHL who achieve less than partial response (PR) following first line platinum-based salvage chemotherapy traditionally have poor outcomes and they represent a big challenge as standard approaches are lacking [16]. Options for such patients include: switching to another non-cross resistant salvage regimen or the use of novel agents such as check point inhibitor or Bv, as monotherapy or in combination. As prospective comparative data is limited, there is no ideal salvage regimen in the treatment of R/R cHL patients, and centers use regimens based on their experiences and comfort. Most regimens are either gemcitabine or platinum based and appear somewhat equivalent with ORR in the range of 60–85% [2,8-10]. In the era of novel agents, choosing a particular salvage regimen became increasingly difficult due to the paucity of prospective comparative data to guide on the optimal approach. Herein we report the outcome of R/R cHL patients requiring ≥ two lines of salvage compared to patients requiring a single line of salvage in the contemporary era of chemo-immunotherapy.

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2. Materials and methods

2.1. Patients' selection and informed consent

The study was ethically approval by King Abdullah International Medical Research Center Institutional Review Board (KAIMRC-IRB) and all methods were carried out in accordance with KAIMRC-IRB guidelines and regulations. The informed consent was waived by KAIMRC-IRB due to the retrospective nature of the study. All patients' ≥ 14 years of age with R/R cHL who received salvage therapy and were potential candidates for HCT at our institution in the period of 2010 – 2018 were identified. Patients were eligible if they had histologically proven evidence of cHL. Achieving a PR or better was an eligibility criteria to proceed with HCT, in addition to having an Eastern Cooperative Oncology Group (ECOG) performance status of II or better. Other requirements and responses were as defined per the International Harmonization Project response criteria [17].

2.2. Salvage chemotherapy and response assessment pre-HCT

Patients received platinum based regimens predominantly ESHAP as first salvage followed by IGEV at the discretion of the treating physician. Bv was added to salvage chemotherapy particularly in patients with remissions following front line of < 12 months. All patients received a minimum of two cycles of salvage. All analyzed patients underwent pre-HCT disease evaluation with PET/CT and/or CT scan, as available. Standardized uptake value of the liver and mediastinum was noted and update classified per Deauville criteria as ≤ liver uptake or ≤ mediastinal blood pool. Patients with update ≤ liver (i.e. Deauville 3) were deemed to have complete metabolic remission (CMR) and those with higher SUV as partial metabolic response (PMR) [18].

2.3. Stem cell collection, HCT and Bv consolidation post HCT

Autologous peripheral blood stem cells were collected by apheresis following recovery from salvage therapy using granulocyte colony stimulating factor (GCSF) and after ensuring lack of bone marrow involvement by disease. Patients received carmusitine, etoposide, cytarabine and melphalan (BEAM) as the conditioning regimen followed by autologous rescue of stem cells. All patients were hospitalized during conditioning therapy and until neutrophil and platelet engraftment. Neutrophil engraftment post HCT was defined as the time to achieve an absolute neutrophil count (ANC) ≥ 500 × 10^9/L for three consecutive days whereas platelet engraftment was defined as the time to achieve a platelet count of ≥ 20 × 10^9/L for seven days independent of transfusions.

Bv consolidation was given starting day 30–45 post HCT for selected patients at 1.8 mg/kg every 3 weeks with dose adjustment as needed with maximum total number of doses delivered pre- and post-HCT of 16. The indication for post HCT consolidation was remission < 12 months or evidence of extra-nodal disease at relapse [19].

2.4. Definitions and statistical methods

Patients obtaining less than a complete remission (CR) within 3 months from the end of first line therapy were deemed refractory, whereas relapsed patients were those who had evidence of disease relapse beyond 3 months. OS was calculated from the date of transplant until the date of death of any cause or last documented follow-up. Progression Free Survival (PFS) was calculated from the time of transplant until death of any cause or evidence of disease progression or relapse. Baseline patient, disease and treatment related variables were reported using descriptive statistics (counts, medians and percentages). Categorical and continuous variables were compared using Pearson's chi-squared and Wilcoxon / Kruskal-Wallis, respectively. Probability of OS and PFS was computed using the Kaplan-Meier method. Group comparisons were made using the log-rank test. Time to event was calculated from the date of transplant until the event of interest or point of last clinical encounter, in which case the event was censored. Cox regression model was used to calculate univariate and multivariate analysis. All variables with p value < 0.2 were entered in the multivariate model. Statistical analyses were performed using JMP Pro-Version 11 (SAS Institute, Cary, NC, USA) software and EZR on R commander, https://www.jmp.com/en_us/home.html.

3. Results

3.1. Baseline characteristics

A total of 55 patients with R/R cHL were identified and included for further analysis. The median age at transplant was 25 (14–57) years, and 30 (55%) were males. The median (range) time to relapse following front line therapy was 7.9 months (0.9–133). A total of 19 (35%) of patients had refractory disease with evidence of progression or relapse within 3 months following completion of front line therapy and 35 (60%) had evidence of disease progression or relapse within 12 months. Thirty three (60%) required one line of salvage, 15 (27%) required two lines, whereas the remaining seven (13%) requires ≥ 3 lines. Thirty (55%) patients received Bv as part of their salvage therapy. Response assessment prior to HCT by PET/CT scans was negative (Deauville ≤ 3) in 31 (56%) and positive in 18 (33%); PET/CT pre-SCT was not performed in six (11%) patients. All patients had evidence of PR or better on CT as pre-requisite to proceed to HCT. Consolidative Bv post HCT was given to 23 (42%) of patients. Baseline characteristics of this cohort are shown in Table 1.

3.2. Baseline characteristics stratified by number of salvage lines

Stratified according to the number of salvage lines prior to HCT, there was no significant difference found with regards to gender, proportion of refractory disease or time to relapse. In cases requiring ≥ two salvage lines prior to HCT, patients were significantly younger at HCT, median (range) 22 (14–49) vs. 31 (15–57) years (p= 0.041). received Bv more often as part of salvage chemotherapy 16 (73%) vs. 14 (42%) (p= 0.025). Those requiring ≥ two salvage lines prior to HCT also received post HCT Bv consolidation; however, with no statistical significance 13 (59%) vs. 10 (30%) (p= 0.1). The median (range) of total salvage cycles prior to HCT of patients who received single salvage was 2 (2–3) and for those who received ≥ 2 salvage lines was 4 [2–8]. ESHAP was the most commonly used first salvage in both cohorts, albeit with a trend towards higher use in the ≥ 2 salvage lines cohort at 49 vs. 88%, respectively (p=

Table 1
Baseline characteristics of the entire cohort.

Characteristic	*N*= 55 (%)
Male, n (%)	30 (55)
Age at HCT, median (range)	25 (14–57)
Time to Relapse, months (range)	7.9 (0.9–133)
Refractory (≤ 3 months remission)	19 (35)
Relapse ≤ 12 months, n (%)	35 (64)
No. of Salvage Regimens, n (%)	
One	33 (60)
Two	15 (27)
≥ Three	7 (13)
Brentuximab Containing Salvage, n (%)	30 (55)
PET/CT Status pre-HCT, n (%)	
Complete Metabolic Response	31 (56)
Partial Metabolic Response	18 (33)
N/A	6 (11)
Consolidation Bv, n (%)	23 (42)
Median follow up, months (range)	29.5 (1–91.3)

Abbreviations: HCT: hematopoietic stem cell transplant; PET/CT: positron emission tomography / computed tomography; N/A: not available.

0.07). A total of 16 (73%) of patients received Bv with salvage chemotherapy; 2 (10%) in first, 9 (41%) in second and 5 out of 7 (57%) in third. The use of Bv was at the discretion of the treating physician. Further breakdown of salvage regimens used in both cohorts in shown in Table 2.

Proportion of patients with a negative PET/CT prior to HCT was higher among patients requiring one vs. ≥ two lines of salvage at 72% vs. 52%, although not statistically significant (p= 0.14). The median follow up (range) of patients who received single salvage at time of analysis was 21 (1–89) months and for those who received ≥ 2 salvage lines was 30 (0.5–76) months. The baseline characteristics stratified by number of salvage lines pre-HCT are shown in Table 2.

3.3. Treatment outcome and risk factors influencing PFS

On univariate analysis age looking at typical factors that may influence outcome, we found that male gender HR 3.27 (1.17–11.57; p= 0.023), ≥ 2 salvage lines HR 1.97 (0.75–5.25; p= 0.16) and CMR HR 0.24 (0.074–0.67; p= 0.0065) were associated with a p value of < 0.2 and were thus entered into the multivariate model. Male gender HR 4.5 (1.41–19.92; p= 0.0095) and CMR status Prior to HCT HR 0.27 (0.08–0.76; p= 0.013) were significant at the multivariate stage. The univariate and multivariate analysis of different risk factors in relation to PFS are shown in Table 3. Due to limited number of events for OS, a cox model was not possible. The details of Bv consolidation and the toxicities observed are listed in Table 4.

At 2 years, the estimated PFS and OS for patients requiring one vs. ≥ two lines of salvage was 71.2% (50.1–84.7) vs. 51.9% (27.6–71.6), p= 0.16 and 84.6% (63–94) vs. 84% (58–95), p= 0.88, respectively as shown in Fig. 1. Furthermore, the estimated 2-year PFS and OS in patients requiring one vs. ≥ two lines of salvage that were in CMR at the pre-HCT PET/CT was 89.3% vs. 80%, p= 0.45 and 95.2% vs. 80%, p= 0.21. Furthermore, there was a trend towards improved PFS with the use of consolidative Bv in the group that received ≥ 2 lines of salvage with HR 0.26 (0.05–1.24; p= 0.091). Such benefit was further enhanced in this group with the use of Bv pre- and post-HCT HR 0.16 (0.03–0.86; p= 0.034).

Table 2
Patient cohort stratified by number of salvage lines pre-HCT.

Characteristic	Single Salvage (n= 33)	≥ Two Salvage (n= 22)	P value
Male, n (%)	17 (52)	13 (59)	0.58
Age at HCT, median (range)	31 (15–57)	22 (14–49)	0.041
Refractory (≤ 3 months remission)	25 (76)	12 (55)	0.1
Time to Relapse, days (range)	223 (28–3870)	260 (26–3988)	0.87
Relapse ≤ 6 months, n (%)	15 (45)	11 (50)	0.74
Relapse ≤ 12 months, n (%)	20 (61)	17 (77)	0.19
No. of Salvage Regimens			< 0.0001
One	33 (100)	N/A	
Two	N/A	15 (68)	
≥ Three	N/A	7 (32)	
First Salvage Chemo Used, n (%)	16 (49)	17 (77)	0.07
ESHAP	9 (27)	1 (5)	
IGEV-Bv	4 (12)	1 (5)	
ESHAP-Bv	4 (12)	3 (13)	
Other			
Second Salvage Chemo Used, n (%)	N/A	9 (41)	N/A
IGEV-Bv	N/A	7 (32)	
mBEAM	N/A	3 (13.5)	
ICE	N/A	3 (13.5)	
Other			
Third Salvage Chemo Used, n (%)	N/A	4 (57)	N/A
IGEV-Bv	N/A	1 (14)	
BeBv	N/A	2 (29)	
Other			
No. of Salvage Cycles, median (range)	2 (2–3)	4 (2–8)	< 0.0001
PET/CT Status pre-HCT, n (%)	21/29 (72)	11/21 (52)	0.14
Negative (Deauville ≤ 3)	8/29 (28)	10/21 (48)	
Positive			
Bv Part of Salvage, n (%)	14 (42)	16 (73)	0.025
Bv Consolidation, n (%)	10 (30)	13 (59)	0.1
Median follow up, months (range)	21 (1–89)	30 (0.5–76)	0.68

Abbreviations: BeBv: bendamustine, brentuximab vedotin; ESHAP: etoposide, methyleprednisolone, cytarabine, cisplatin; HCT: hematopoietic stem cell transplant; ICE: ifosfamide, carboplatin, etoposide; IGEV, iforsfamide, gemcitabine, etoposide, vinorelbine; mBEAM: mini carmusitine, etoposide, cytarabine and melphalan; PET/CT: positron emission tomography / computed tomography.

4. Discussion

The majority of patients with cHL are cured with initial front line therapy; however a proportion of those with R/R disease can still achieve durable remissions with autologous HCT [20]. Chemo-sensitivity to salvage chemotherapy as well as status of disease pre-HCT particularly via PET/CT, are important predictors of outcome. Using the Center for International Blood and Marrow Transplantation Research (CIBMTR) registry using data derived from 728 HCT cases for R/R cHL, resistance to salvage chemotherapy was noted to be an important adverse risk factor [3]. Prior to the era of novel therapies, Villa et al., demonstrated that patients with transplant eligible R/R cHL that require more than one line of salvage to achieve disease control have a poor outcome [16]. Our aim from this analysis is to examine again the outcome of those patients where novel therapy was used as part of salvage and/or consolidation therapy.

With the advent of novel agents, combinations including Bv with chemotherapy or checkpoint inhibitors have emerged and appear to have a favorable safety profile as well as higher CMR rates around 80%. PDL1 blockade with checkpoint inhibitors nivolumab and pembrolizumab had shown significant single-agent activity in RR cHL [21–23] . More recently, combination of the checkpoint inhibitor with brentuximab was found to be active and well tolerated in RR cHL [24]

A number of groups have shown that Bv can feasibly be combined with ESHAP, IGEV, DHAP and bendamustine among others [12–15]. Such combinations carry important implications for two reasons; first,

Table 3
Univariable and multivariable risk factors influencing progression free survival.

PFS	Univariable HR (95% CI; P value)	Multivariable HR (95% CI; P value)
Age at HCT	1.0003 (0.96–1.04; p= 0.99)	
Age > Median	0.65 (0.23–1.67; p= 0.38)	
Male Gender	3.27 (1.17–11.57; p= 0.023)	4.5 (1.41–19.92; p= 0.0095)
Refractory Disease	0.9 (0.29–2.38; p= 0.83)	
Remission < 6 months	0.55 (0.19–1.41; p= 0.22)	
Remission < 12 months	0.94 (0.37–2.7; p= 0.91)	
≥ 2 Salvage Lines	1.97 (0.75–5.25; p= 0.16)	2.19 (0.78–6.65; p= 0.14)
Bv Part of Salvage	1.75 (0.67–4.84; p= 0.25)	
Bv Consolidation	0.77 (0.27–2.04; p= 0.61)	
CMR pre-HCT	0.24 (0.074–0.67; p= 0.0065)	0.27 (0.08–0.76; p= 0.013)

Abbreviations: Bv: brentuximab vedotin; CI: confidence interval; CMR: complete metabolic response; HCT: hematopoietic stem cell transplant; HR: hazard ratio.

Table 4
Brentuximab consolidation and observed adverse events.

Characteristic	*N*= 23 (%)
Indication for Bv Consolidation, n (%)	
Remission < 12 Months	16 (70)
Extranodal Relapse	7 (30)
Total Doses of Bv Delivered, median (range)	12 (3–16)
Neutropenia (≥ Grade 3)	9 (23)
Filgrastim Given During Bv Consolidation, n (%)	9 (23)
Peripheral Neuropathy on Consolidation, n (%)	
Grade I	3 (13)
Grade II	3 (13)
Grade III	1 (4)
Bv Dose Reduced Due to AE	6 (26)

Abbreviations: Bv, brentuximab vedotin; AE, adverse event.

deeper responses particularly CMR prior to HCT is an important goal to attain as eluted to above. Second, highly refractory patients whom are chemo-resistant to salvage therapy such as the group presented herein historically have poor outcomes. Thus, such incorporation of novel agents may salvage a subset of those patients allowing them to proceed to HCT. This is in fact what we observed in our series, where almost three quarters of them received Bv as part of salvage chemotherapy and about half were in CMR pre-HCT. Interestingly, patients in CMR pre-HCT have almost identical outcomes irrespective of the number of salvage lines. Thus deepening the response prior to transplant should be a sought after goal and this will likely be achieved with fewer cycles of salvage chemotherapy if combined with Bv. The incorporation of different novel agents, including PDL1 inhibitors, could potentially replace the cytotoxic chemotherapy while maintaining efficacy. In our series, this permitted the entire group that required two or more lines of therapy to undergo transplantation. In fact, after observing such responses, our center started incorporating Bv as part of first salvage in most patients with early relapse within 12 months following front line therapy.

Our results compare favorably to the series by Villa et al., where among 19 patients requiring second line mini-BEAM, only 9 managed to proceed to HCT with a median post-transplant PFS of only 4 months. Although the outcome in our series was statistically similar between receiving one vs. ≥ two lines of salvage, the outcome of the former was higher as expected from the latter with a PFS of 71.2% (50.1–84.7) vs. 51.9% (27.6–71.6), p= 0.16. On the other hand, OS was similar indicating that these patients despite the high risk nature of their disease were still salvageable with subsequent therapy. x In the current study, Bv incorporation in first or second salvage, although non-structured, had possibly lead to an improvement in overall outcome of R/R cHL and potentially ameliorated the historical difference in outcome between those who needed ≥ two lines of salvage compared to those needing only one. We observed that patients requiring ≥ two lines of salvage prior to HCT can achieve comparable outcomes to those requiring a single line of salvage, particularly if CMR status was attained prior to transplant. Furthermore, early consolidation after HCT is known to improve the PFS in high risk R/R cHL patients [26]. In the present study, 23 (42%) received consolidation Bv post SCT including 13 (59%) of those requiring ≥ 2 salvage lines. We observed the improved PFS in the latter group particularly in those that received Bv pre-HCT i.e. a sandwich approach.

This analysis carries important limitations, particularly with regards to single center design and the possibility that the lack of statistical difference in OS and PFS between those requiring one vs. ≥ 2 salvage lines could be due to the small sample size. Nonetheless, a number of important points are worth highlighting. First, we noted that many patients requiring multiples lines of salvage therapy can respond favorably including attaining CMR status pre-HCT. Second, outcome of those requiring multiple salvage lines is similar especially if in CMR pre-HCT, indicating that the number of lines of salvages carries less significance than the response attained pre-SCT particularly in measure via PET/CT. Finally, a sandwich Bv approach appeared to offer the best outcome in such high risk patients. These results have important implications as such patients may not be referred for HCT given the historically reported poor outcomes. Given the limitations of such analysis, these findings should be further examined.

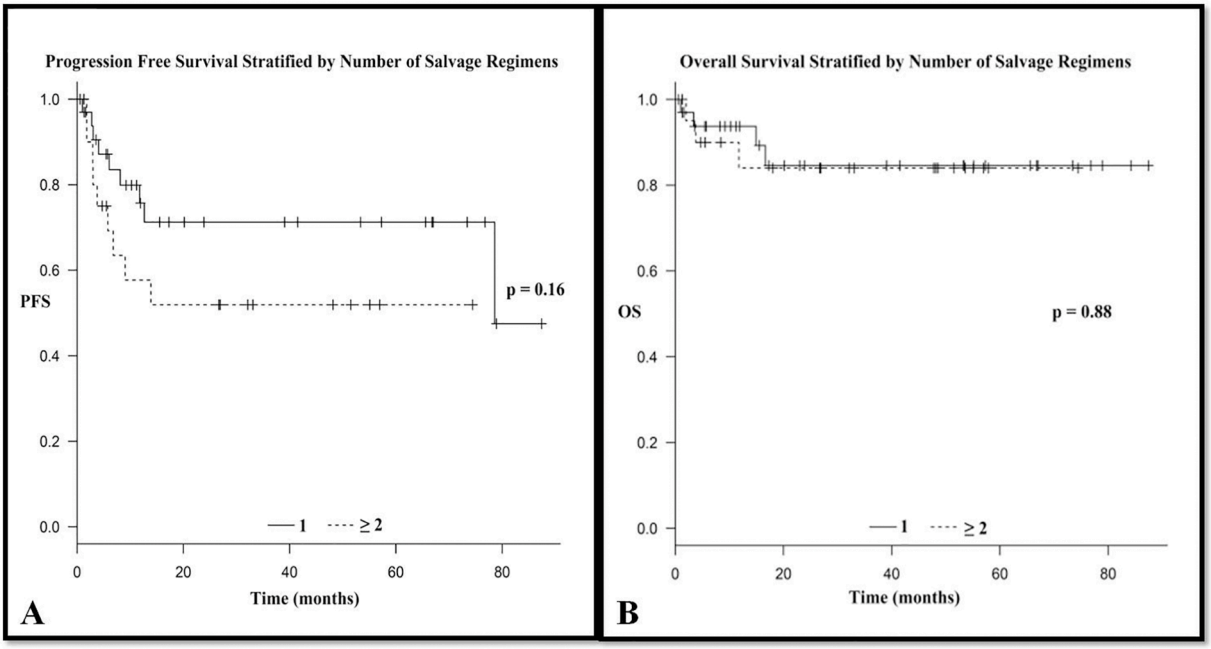

Fig. 1. Estimated two-year progression and overall survival for patients requiring one vs. ≥ two salvage chemotherapy lines: At 2 years, the estimated PFS (A) and OS (B) for patients requiring one vs. ≥ two lines of salvage was 71.2% (50.1–84.7) vs. 51.9% (27.6–71.6), p= 0.16 and 84.6% (63–94) vs. 84% (58–95), p= 0.88, respectively.

Author contributions

KAA: Conceptualization, Methodology, Data acquisition, Writing-Original draft preparation

SG: Conceptualization, Data acquisition, Writing-Original draft preparation

BA: Writing-Reviewing and editing

AA: Writing-Reviewing and editing

AA: Supervision Writing-Reviewing and editing

MA: Supervision, Writing-Reviewing and editing

MD: Conceptualization, Supervision, Data acquisition, Formal analysis, Writing-Reviewing and editing

Declaration of Competing Interest

The authors declare no conflict of interest.

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