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– ORIGINAL PAPER –

The Benefit of Brentuximab Vedotin and Checkpoint Inhibitors in Relapsed/Refractory Hodgkin Lymphoma: A Single-Center Retrospective Study

Diana-Marina FORTOES [2]*, Elena NICORICI[2], Cosmin MINCIUNA [1,2], Andrei CIANGA [1,2], Ramona TIMOFTE[2], Amalia TITIEANU[2], Elena DOLACHI-PELIN[2], Ion ANTOHE [1,2], Angela DASCALESCU[1,2], Catalin DANAILA[1,2]

Abstract

Aim: *To assess the real-world efficacy of brentuximab vedotin and PD-1 inhibitors versus historical chemotherapy-only salvage regimens in relapsed/refractory classic Hodgkin lymphoma.*

Methods: *Retrospective, single-center study of two cohorts (n=30 each) treated between 1996–2012 (historical) and 2017–2021 (immunotherapy), with survival endpoints (OS, PFS, EFS1-3) analyzed by Kaplan–Meier and log-rank tests.*

Results: *The immunotherapy group achieved a higher overall response rate (80% vs. 36.7%, p=0.001), longer median OS (47 vs. 30 months) and superior EFS1–3 (33 vs. 16 months, 32.5 vs. 8 months, 38 vs. 23 months; all p<0.05) compared to historical controls.*

Conclusion: *Incorporation of brentuximab vedotin and PD-1 blockade before and after autologous SCT significantly improves response and survival outcomes in relapsed/refractory Hodgkin lymphoma, supporting earlier use of these agents in salvage and frontline settings.*

Key words: *refractory/relapsed Hodgkin lymphoma , brentuximab vedotin, PD-1 inhibitors, Autologous stem cell transplant (autoSCT)*

[1] University of Medicine and Pharmacy "Gr. T. Popa", Iasi, Romania

[2] Haematology Department, Regional Oncology Institute, Iasi, Romania

Corresponding author:
***Diana-Marina FORTOES,** Haematology Department, Regional Oncology Institute, Iasi, Romania
Email: fortoes.dm@gmail.com

Andrei CIANGA, ORCID: 0000-0003-3215-2562

Amalia TITIEANU, - ORCID: 0000-0001-7088-6511

Angela DASCALESCU, - ORCID: 0000-0001-5388-1583

Introduction

The treatment landscape of Hodgkin lymphoma (HL) has seen exponential progress with the increasingly profound understanding of the biology of the tumor cell and, equally important, its interaction with the microenvironment. Most patients with classic HL (cHL) are cured with combination chemotherapy, but a varying percentage will experience relapses, ranging from 10-15% in early stages to 15-30% in patients with advanced disease[1], [2]. Moreover, another 5-10% of cases will present primary refractory disease. For eligible patients

with chemosensitive disease, autologous stem cell transplant (autoSCT) can provide long-term remission in approximatively half of cases. AutoSCT ineligible patients and chemorefractory cases are facing a paucity of treatment options and, ultimately, a dismal prognosis. For many years, the lack of potent and well-tolerated salvage regimens has represented a major unmet need in the management of relapsed/refractory cHL[3]. The treatment landscape of relapsed/refractory(R/R) cHL has evolved significantly over the past decade following the approval of brentuximab vedotin (BV), as well as that of the PD-1 inhibitors nivolumab and pembrolizumab. The addition of BV to the therapeutic arsenal for R/R cHL has yielded overall response rates of up to 75%, including complete remission in 34% of patients. This has provided an effective and less toxic alternative as a bridging option to autoSCT[3], [4]. This study aims to evaluate the efficacy of BV and Pembrolizumab and Nivolumab in a real-world cohort of patients, by comparing their outcomes with those of a historical cohort managed at the same institution prior to the introduction of immunotherapy.

Material and method

Two cohorts of 30 patients each, diagnosed with R/R cHL between 1996 to 2012 and 2017 to 2021, respectively, and treated in the Hematology Department of the Regional Institute of Oncology Iasi, were included in this restrospective, single-center study. The first group is a historical one, in which patients received only standard chemotherapy and had limited access to autoSCT. The second group benefited of immunotherapy with BV and anti-PD-1 agents at relapse. Along this article we will refer to the two groups as „immunotherapy group" for the patients that received BV and PD-1 inhibitors, and „historical group" for the ones that received only standard chemotherapy. The patients were diagnosed through histopathological and immunohistochemical analysis of a lymphadenopathy obtained via excisional biopsy. The staging of disease was based on Ann-Arbor criteria, and the prognosis was assessed using EORTC risk stratification criteria for stages I and II and the International prognostic score (IPS) for advanced disease. The statistical analysis was performed using IBM SPSS Statistics 26.0 Software. A p value <0.05 was considered to be statiscally significant. Overall survival (OS), event free survival and progression-free survival (PFS) were estimated using the Kaplan Meier method. The log rank test was used for comparisons of Kaplan-Meier curves. OS was defined as the time, in months, from diagnosis to death from any cause. PFS was defined as the time, in months, from the achievement of a type of response to the occurence of progressive disease, last follow-up or death from any cause. Given the heterogeneity of chemotherapy regimens administered in the historical cohort across multiple lines of therapy, a direct comparison of the impact of immunotherapy on survival required the definition of three distinct endpoints: Event-free survival 1, 2, and 3 (EFS1, EFS2, EFS3). These were defined as the time, in months, from the first, second, and third relapse—or from the documentation of refractory disease at each corresponding point—until death from any cause, or last follow-up.

Results

Patient Cohort and Treatment Characteristics

We studied 60 patients with cHL with baseline characteristics at time of diagnosis and general treatment and response outcomes summarized in Table I. The median age at diagnosis was 29 years (range, 16-78 years). The median follow-up duration was 18 months.

The Immunotherapy Group

A total of 30 patients with R/R cHL were included in this group. All patients received BV at some point during their disease course—either at first relapse, in subsequent lines of therapy, or as maintenance following autoSCT. At the time of first relapse (second line therapy, n = 30), salvage regimens were distributed as follows: 11 patients (37%) received DHAP (Dexamethasone, Cytarabine, Cisplatin), 5 (16%) received IGEV (Ifosfamide, Gemcitabine, Vinorelbine), 3 (10%) received BV monotherapy, and 8 (27%) received other salvage regimens. Furthermore, 9 patients (30%) underwent salvage treatment with BV followed by ASCT.

At second relapse (line III; n = 20), 12 patients (80%) were treated with BV and 3 patients (20%) received Nivolumab. At third relapse (line IV; n = 13), treatment distribution was: 4 patients (30%) on BV, 3 (23%) on Nivolumab, and 6 (47 %) on Pembrolizumab. Additionally, 10 patients (33%) received BV as maintenance therapy post-ASCT.

The Historic Group

The entire group was treated with standard regimes of chemotherapy varing from ABVD to COPP and BEACOPP in first line and at relapse with various regimes in conformity with protocols and studies at the time.

Patient characteristics	Historic group (n=30)	Immunotherapy group (n=30)
Sex, n(%)		
Male	14 (46.7)	17 (56.7)
Female	16 (53.3)	13 (43.4)
Age		
Median age at diagnosis (years)	31	28.9
Median period of follow-up after first relapse (months)	16	33
Stage of disease at diagnosis n(%)		
I - II	12 (40)	9 (30)
III - IV	18 (60)	21(70)
Prognostic categories, n(%)		
Favorable	19 (63.3)	20 (66.7)
Unfavorable	11 (36.7)	10 (33.3)
Early relapse (<12 months), n(%)	20 (66.7)	19 (63.3)
Type of salvage treatment at relapse	COPP/ DHAP/GemOX and other Gemcitabine based protocols	GVD/ ICE/ IGEV/DHAP/BeIGEV/GemOX alone or followed by ASCT with or without maintenance with BV; Nivolumab, Pembrolizumab
Autologous stem cell transplant, n(%)	6 (20)	17 (56.7)
Allogeneic stem cell transplant, n(%)	0	2 (6)

Table 1. *Patient caracteristics in study group*

Treatment outcome and survival analysis

At the last follow-up, 11 of 30 patients in the historical group (36.7%; 11/30; 95% CI: 21.9–54.5 %) had achieved complete or partial response compared with 24 of 30 patients in the immunotherapy group (80%; 24/30; 95% CI: 62.7–90.5%). This difference in overall response rate (ORR) was statistically significant, 43.3% (95 % CI: 20.9–65.7 %; p = 0.001).

Median OS considered from the moment of diagnosis was 30 months in the Historical group versus 47 months in the Immunotherapy group. The median overall survival after the first relapse (EFS1) was 16 months compared with 33 months, respectively (p = 0.028). Focusing on survival from the time of second relapse (EFS2) in the Historical group, median survival was 8 months, whereas in the Immunotherapy group it was 3.5 months.

In each group, 22 patients experienced a second relapse, and out of these, 13 (32 %) in the first group and 15 (50 %) in the second group went on to a third relapse.The median EFS from the time of third relapse (or refractory disease) to death or last follow-up (EFS3) was 23 months for the first group and 38 months for the second one (p = 0.03) (Table II).

Outcome	Historical group (n)	Immunotherapy group (n)	Median (months)	p-Value
Overall survival	22 (73.3%)	23 (76.7%)	30 vs. 47	**0.258**
Event free survival after first relapse (ES1)	—	—	16 vs. 33	**0.028**
Event free survival after second relapse (ES2)	—	—	8 vs. 32.5	**0.039**

Event free survival after third relapse (ES3)	—	—	23 vs. 38	**0.03**
Patients at second relapse	22 (55 %)	22 (73%)	—	—
Patients at third relapse	13 (32 %)	15 (50 %)	—	—

***Table 2**. Survival outcomes. ES1, ES2, ES3- the time, in months, from the first, second, and third relapse—or from the documentation of refractory disease at each corresponding point—until death from any cause, or last follow-up.*

For patients who received Brentuximab as maintenance (n = 10), the median PFS was 15 months (95 % CI: 2.6–27.4), compared to 6 months (95 % CI: 4.0–8.0) in the non-maintenance group (n=20). Mean PFS was also longer with maintenance (21.1 vs. 8.5 months). At 12 months, 7 of 10 patients (70 %) in the maintenance arm remained progression-free, compared with 4 of 20 patients (20 %) without maintenance. The median PFS was 15 months (95 % CI: 2.6–27.4) with maintenance versus 6 months (95 % CI: 4.0–8.0) without, and mean PFS was 21.1 versus 8.5 months. Although the Kaplan–Meier curve for maintenance clearly shows superior 12-month PFS, the difference did not reach statistical significance (p = 0.170) (Figure 1).

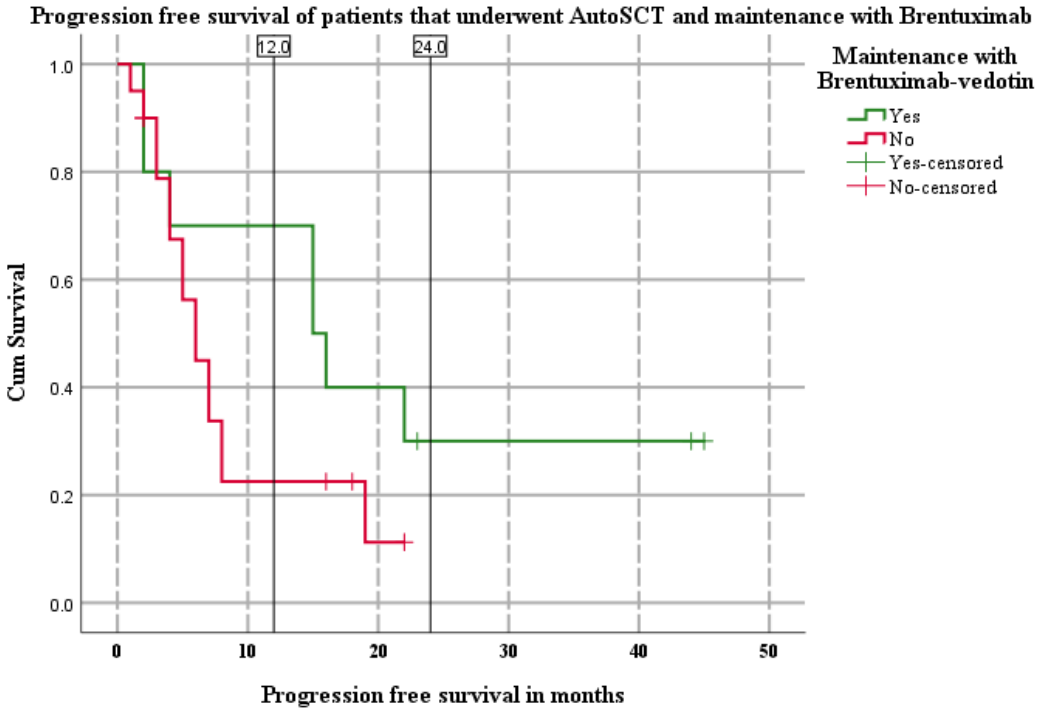

***Figure 1.** Progression free survival of patients that underwent AutoSCT and maintenance with Brentuximab vedotin*

Discussions

The treatment landscape of relapsed/refractory (R/R) cHL has evolved significantly over the past decade following the approval of brentuximab vedotin (BV), an anti-CD30 antibody-drug conjugate, and the PD-1 inhibitors nivolumab and pembrolizumab. These agents have significantly expanded options for salvage therapy prior to autologous hematopoietic cell transplantation (AHCT), posttransplant maintenance, and treatment of relapse after AHCT, which have led to improved survival in the modern era.[5]

The marked improvement in response rates and survival observed in our immunotherapy cohort mirrors findings from the studies, which have established brentuximab vedotin (BV) and PD-1 inhibitors as transformative agents in R/R (cHL)[6], [7]. In our series, the immunotherapy group achieved an overall response rate (ORR) of 80% and a complete response rate (CR) of 57 % at the last follow-up, compared with 36.7 % and 10 %,

respectively, in the historical cohort (p = 0.001)—consistent with single-arm trials demonstrating ORRs of 65–95 % for PD-1 inhibitor–containing salvage protocols[8].

The median overall survival after first relapse (EFS1) in our immunotherapy group was 33 months versus 16 months in the historic group (p = 0.028), aligning with reports that post-ASCT BV maintenance and checkpoint blockade can extend median survival beyond 30 months in relapsed cHL. Furthermore, our median EFS2 of 32.5 months in Immunotherapy group after second relapse significantly exceeds the 7–12 month benchmark historically reported for chemotherapy-only salvage regimens[6], [9]. Finally, the improvement in median EFS3 to 38 months with immunotherapy (versus 23 months in the historic group, p = 0.03) underscores the critical role of BV- and PD-1–based strategies in patients who are refractory to second-line therapy or experience a third relapse[1]. Notably, while autologous stem cell transplantation (ASCT) contributes significantly to EFS1, the survival advantage of the immunotherapy cohort diminishes with each successive treatment line, highlighting the need to deploy these novel agents earlier—and, optimally, in combination—to maximize efficacy and minimize toxicity. Incorporation of these agents into frontline chemotherapy regimens is feasible, and early results from a Phase III trial of nivolumab-AVD compare favorably with the existing standard for advanced stage HL, brentuximab vedotin plus AVD[6]. The safety profile of BV and checkpoint blockade compares favorably with that of multiagent salvage chemotherapy[10]. Conventional regimens such as DHAP or ICE carry high rates of grade 3–4 hematologic toxicity—neutropenia with life-threatening sepsis and thrombocytopenia in up to 30 % of cycles and occasional renal toxicity leading to treatment discontinuation[11], [12]. Overall, our data corroborate the growing body of evidence that incorporating BV and checkpoint inhibitors into salvage algorithms substantially enhances both response durability and long-term survival in relapsed/refractory cHL.

Conclusion

Our real-world comparison confirms that integrating brentuximab vedotin (BV) and PD-1 inhibitors into salvage regimens substantially outperforms historical, chemotherapy-only approaches in relapsed/refractory cHL. Even among patients refractory after second-line therapy or following a third relapse, median OS improved, underscoring the durable benefit of immunotherapy. These findings, along with evidence from multiple clinical trials, suggest that introducing these agents earlier in the treatment course—whether in early salvage or frontline settings in combination with chemotherapy—may further enhance therapeutic outcomes.

Ethics Statement and Conflict of Interest Disclosures
Financial support and sponsorship: All authors have declared that no financial support was received from any organization for the submitted work.

Ethics Consideration
The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national laws. Written informed consent was provided by all participants in this study.

Conflict of interest:
No known conflict of interest correlated with this publication.

Availability of data and materials
The data used and/ or analyzed throughout this study are available from the corresponding authors upon reasonable request.

Competing interest
The authors declared that they have no competing interests.

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