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Impact of Hematopoietic Stem Cell Transplantation on PD-1 Blockade Efficacy in Relapsed/Refractory Hodgkin's Lymphoma

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Abstract: Background: Classical Hodgkin lymphoma (cHL) is a treatable malignancy; however, relapsed or refractory (R/R) cases pose significant challenges. PD-1 inhibitors have shown efficacy, but the role of hematopoietic stem cell transplantation (HSCT) following PD-1 blockade remains uncertain. This study aims to evaluate the impact of HSCT after PD-1 blockade on progression-free survival (PFS) and overall survival (OS) in patients with R/R cHL. Methods: We conducted a multicenter, retrospective study involving 42 patients with R/R cHL who received PD-1 inhibitors between 2016 and 2021. Patients were categorized into two groups: those who underwent HSCT after PD-1 therapy (n = 19) and those who continued PD-1 inhibitors without HSCT (n = 23). Results: Among the 42 patients, 27 achieved complete remission (CR) and 15 achieved partial remission (PR) following PD-1 blockade. In the HSCT group, 92% of patients remained progression-free at 3 years, compared to 65% in the non-HSCT group (p = 0.021). OS rates were similar between groups (100% vs. 96%, p = ns). Notably, 80% of PR patients in the HSCT group converted to CR. Relapse rates were significantly lower in the HSCT group (5%) compared to the non-HSCT group (43%, p = 0.005). Conclusions: HSCT following PD-1 blockade enhances PFS in patients with R/R cHL, particularly among those with PR, without offering a significant OS benefit. Further research is warranted to optimize treatment strategies for this patient population strategies.

Keywords: classical Hodgkin lymphoma (cHL); PD-1 blockade; hematopoietic stem cell transplantation (HSCT); relapsed/refractory (R/R) lymphoma; progression-free survival (PFS)

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1. Introduction

Classical Hodgkin lymphoma (cHL) is highly curable with standard treatments [1]. In patients with relapsed or refractory (R/R) cHL, salvage therapy followed by autologous hematopoietic stem cell transplantation (HSCT) can induce prolonged remissions. However, patients who relapse after auto-HSCT have a poor prognosis, with a median overall survival (OS) ranging from 10 to 28 months in the prebrentuximab vedotin era [1–5].

Brentuximab vedotin is an antibody–drug conjugate targeting CD30, a cell surface protein expressed by Hodgkin lymphoma cells. This treatment has significantly improved outcomes in R/R cHL patients, demonstrating high overall response rates (ORRs), with some patients achieving complete remission. Brentuximab vedotin is approved for use in patients who have relapsed or are refractory to standard treatments, particularly after failure of autologous HSCT. However, while brentuximab vedotin offers substantial benefits, it is not curative for the majority of patients, with only around 20% achieving long-term remission with this single-agent therapy [6]

Checkpoint inhibitors (CPIs) have significantly improved the prognosis of patients with R/R cHL, demonstrating exceptional outcomes even in heavily pretreated patients. Despite these promising results, there are limited data on the long-term efficacy of Programmed Death-1 (PD-1) blockade, as the median follow-up in previously published studies has been relatively short [7–15].

Despite the remarkable immediate efficacy of PD-1 blockade, many questions remain unanswered regarding optimal management, including treatment duration, long-term efficacy, and the potential need for consolidation with autologous or allogeneic HSCT [13,16–20].

This study aims to explore the role of HSCT consolidation in patients who respond to PD-1 blockade, assessing its impact on progression-free survival (PFS) and overall survival (OS) in a real-world, multicenter cohort.

2. Materials and Methods

This retrospective study included 42 patients with relapsed/refractory classical Hodgkin lymphoma (R/R cHL) who were treated with PD-1 inhibitors between 2016 and 2021. Patients achieved either partial remission (PR) or complete remission (CR). A total of 19 patients (45%) underwent hematopoietic stem cell transplantation (HSCT) after PD-1 therapy, while 23 (55%) continued with PD-1 inhibitors. Clinical data were collected from the Apulian hematology network (REP), which encompasses several Italian centers. PD-1 inhibitors were administered as monotherapy, and patients had a median of four prior treatments before receiving PD-1 blockade. Various patient characteristics, including prior stem cell transplantation and response to PD-1 therapy, were analyzed (Table 1).

This study enrolled 42 patients between 2016 and 2021, with a median age of 32 years (range 19–75). At the start of PD-1 treatment, 25 out of 42 (59%) patients had stage III or IV disease. PD-1 inhibitors were initiated a median of 28 months (range 7–223) after the initial diagnosis of cHL, with a median of four previous lines of treatment (range 3–7). Prior to PD-1 therapy, 23 out of 42 patients (55%) had undergone autologous HSCT, and 4 (9%) had undergone allogeneic HSCT. All patients received brentuximab vedotin (BV) prior to PD-1 blockade, and PD-1 inhibitors were administered as a single-agent therapy.

In the allogeneic HSCT group, conditioning regimens were fludarabine-based, and T-cell depletion of the graft was performed in 6 out of 12 (50%) cases by in vivo T-cell depletion using thymoglobulin (5 mg/kg). Graft-versus-host disease (GVHD) prophylaxis was achieved using cyclosporine alone in 3 out of 12 (25%) cases and cyclosporine plus methotrexate in 8 out of 12 (67%) cases. All patients underwent reduced-intensity conditioning (RIC), with 10 (83%) receiving grafts from a matched sibling donor (MRD) and 2 (17%) from a matched unrelated donor (MUD).

The study protocol was approved by the Institutional Review Board (IRB), and data were extracted from medical records by a co-investigator at each participating institution. All patient data were de-identified before inclusion in the analysis.

Table 1. Patient Characteristics.

Characteristic	HSCT (*n* = 19)	No HSCT (*n* = 23)	*p*
Total	19 (45%)	23 (55%)	-
Median age, y (range)	31 (19–60)	48 (21–75)	0.003
B symptoms (%)	10 (53%)	16 (70%)	0.073
Stage 3–4 (%)	11 (58%)	14 (61%)	0.222
Median previous CHT lines (range)	4 (3–6)	4 (3–7)	0.899
Type of CPI:			
Nivolumab (%)	14 (74%)	16 (70%)	0.769
Pembrolizumab (%)	5 (26%)	7 (30%)	0.843
Previous SCT:			
Autologous (%)	12 (63%)	11 (48%)	0.320
Allogeneic (%)	0 (0%)	4 (17%)	0.056
Type of SCT after CPI:			
Autologous (%)	7 (37%)	-	-
Allogeneic (%)	12 (63%)	-	-
Median number of CPI cycles (range)	12 (12–66)	31 (24–106)	0.007
Response to CPI:			
CR (%)	9 (47%)	18 (78%)	0.038
PR (%)	10 (53%)	5 (22%)	0.061

Abbreviations: CHT = chemotherapy; SCT = stem cell transplantation; CPI = checkpoint inhibitors; CR = complete remission; PR = partial remission.

2.1. Study Endpoints

The primary endpoint of this study was to evaluate the progression-free survival (PFS) of patients with R/R cHL who responded to PD-1 inhibitors in relation to the different treatment strategies employed. Secondary endpoints included the relapse rate and overall survival (OS) of patients.

2.2. Response Criteria and Statistical Analysis

Response was assessed by positron emission tomography (PET) according to the refined Lugano Classification response criteria.21 CR was defined as the complete disappearance of all detectable clinical evidence of disease and any disease-related symptoms that were present before therapy. PR was defined as at least a 50% decrease in measurable disease with no new sites. Stable disease (SD) was defined as a failure to meet the criteria for CR or PR but not fulfilling the criteria for progressive disease (PD). PD was defined as the appearance of any new lesion or an increase of 50% in previously involved sites from nadir. Indeterminate response (IR) was used to identify lesions that needed further clarification until confirmed as flare/pseudo-progression or true PD. The first response after four infusions of PD-1 inhibitor was evaluated, and, in the case of an indeterminate response according to the Lugano criteria, the subsequent response was assessed.

PFS was defined as the time interval between initiation of PD-1 inhibitor therapy and disease progression or death from any cause. OS was measured from the initiation of PD-1 inhibitor therapy until death from any cause or last follow-up. Efficacy and safety data were assessed descriptively. Survival curves were generated using the Kaplan–Meier method and analyzed with SPSS software version 28. Patients lost to follow-up were censored at the date of their last known follow-up visit.

3. Results

In this study, 42 patients with partial remission (PR) or complete remission (CR) after PD-1 blockade therapy were included. Among them, 19 patients (45%) underwent hematopoietic stem cell transplantation (HSCT) after PD-1 therapy, while 23 patients (55%) continued with PD-1 inhibitor therapy without subsequent HSCT.

A breakdown of the clinical responses and outcomes for these 42 patients is provided in Table 2, grouped according to whether they had prior HSCT. The 23 patients who had previously undergone autologous HSCT (auto-HSCT) were further divided into two subgroups: 12 patients who received an additional allogeneic HSCT (allo-HSCT) and 11 patients who did not undergo further HSCT. In the group of 12 patients who had allo-HSCT after CP) treatment, 6 achieved complete remission (CR), while the remaining 6 had partial remission (PR). Among these six patients in PR, four eventually achieved CR, and two showed disease progression. Of the 11 patients who did not receive further HSCT, 10 achieved CR, although 2 relapsed, with 1 responding to retreatment. One patient experienced PR but ultimately faced disease progression and death.

Table 2. Clinical Response and Treatment Performed (Total 42 Patients).

Group	Response to CPI	Outcome
Previous auto-HSCT (*n* = 23)		
12 allo-HSCT	6 CR	6 CR
	6 PR	4 CR, 2 progression
11 no-SCT	10 CR	8 CR; 2 relapses (retreatment CR)
	1 PR	1 progression (1 death)
No previous HSCT (*n* = 15)		
7 auto-HSCT	3 CR	2 CR; 1 relapse (retreatment SD)
	4 PR	4 CR
8 no SCT	8 CR	7 CR; 1 relapse (retreatment PR)
Previous allo-HSCT (*n* = 4)		
4 no further SCT	4 PR	3 stable disease (1 death), 1 progression (1 death)

Abbreviations: HSCT = hematopoietic stem cell transplantation; CPI = checkpoint inhibitors; CR = complete remission; PR = partial remission; SD = stable disease.

Among the 15 patients with no prior HSCT, 7 had undergone autologous HSCT and 8 had not received any HSCT. In the autologous HSCT subgroup, three patients achieved CR, while four had PR, with two experiencing relapses and one requiring retreatment for SD. In the subgroup of eight patients who had not undergone any HSCT, all achieved CR, although one patient relapsed and was subsequently treated with PD-1 inhibitors, achieving PR. The final group consisted of four patients with prior allogeneic HSCT, all of whom had PR. Among them, three patients experienced stable disease, while one experienced disease progression and died. These results underline the diverse responses and outcomes based on the type of prior HSCT and treatment regimens.

Regarding demographics, patients in the HSCT group were notably younger, with a median age of 31 years, compared with 48 years in the non-HSCT group ($p = 0.003$). Additionally, the non-HSCT group had a higher rate of complete remission (78% vs. 47%, $p = 0.038$).

At a median follow-up of 38 months (range 12–67 months) after HSCT, the relapse rate in the HSCT group was low, with only one patient (5%) relapsing after 12 months

post-autologous HSCT. Notably, 8 out of 10 patients who were in PR before HSCT converted to CR after the procedure and remained in remission (see Table 2). In the subgroup of seven patients who received autologous HSCT without a prior transplant, six remained in CR, while one patient who had been in CR before HSCT relapsed but responded to retreatment with PD-1 inhibitors, achieving stable disease.

In the allo-HSCT group, six patients were in CR and six in PR at the time of transplantation. Post-transplant, 10 patients (83%) achieved CR, with only 2 patients (17%) experiencing disease progression. Among the 10 who achieved CR after allo-HSCT, none relapsed, although 3 (25%) developed acute graft-versus-host disease (aGVHD), including one case of grade III-IV aGVHD. Additionally, six patients (50%) developed chronic GVHD, with four having limited chronic GVHD and two experiencing extensive chronic GVHD. The median time from the last PD-1 dose to allo-HSCT was 4 months (range 2–6 months), and of these patients, three developed acute GVHD—two of them within 2–4 months post-transplant and one after 6 months. Of note, one patient developed grade III-IV aGVHD within 3 months, suggesting a more severe form of the disease.

In contrast, the four patients in the non-HSCT group who had undergone prior allo-HSCT did not develop GVHD after receiving PD-1 inhibitors, indicating a lower risk of GVHD in those who did not undergo further HSCT after their initial transplant.

In the non-HSCT group (Figure 1), at a median follow-up of 42 months (range 14–89 months), 15 out of 18 patients (83%) who achieved CR after PD-1 blockade remained in remission. However, three patients (17%) relapsed and were retreated with the same PD-1 inhibitor. Of these three, two achieved subsequent CR, while one attained stable disease. Among the five patients in PR, three continued the same PD-1 therapy, maintaining stable disease (one of these patients later died from an infection), while two switched to other therapies and died due to lymphoma progression.

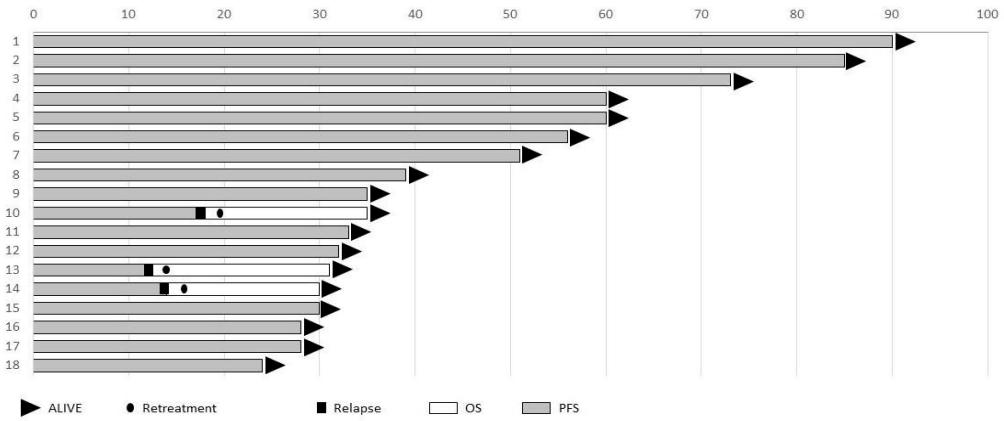

Figure 1. Outcome of patients after CPI discontinuation (no HSCT group).

An analysis of clinical features revealed significant differences between the groups. The patients who received HSCT post-CPI treatment were significantly younger ($p = 0.003$), possibly reflecting a preference for younger patients who can tolerate intensive treatments like HSCT. The distribution of advanced disease (stages 3–4) was similar between the two groups, indicating comparable disease severity. However, the non-HSCT group had a higher incidence of B symptoms (70% vs. 53%), though this difference was not statistically significant ($p = 0.073$). The number of prior chemotherapy lines was similar between groups ($p = 0.899$), showing that patients had comparable pretreatment histories. Overall, patients in the HSCT group appeared to have better disease control, as reflected by a higher rate of CR (47% vs. 78%).

The median time to CR was 6 months (range: 4–12 months) in the HSCT group, with 25% of patients reaching CR in 5 months and 75% in 9 months. In the non-HSCT group, the median time to CR was 8 months (range: 5–14 months), with 25% reaching CR at 6 months and 75% at 11 months.

At the 3-year follow-up (Figures 2 and 3), progression-free survival (PFS) was significantly higher in the HSCT group (92%) compared with the non-HSCT group (65%) (p = 0.021), although there was no significant difference in overall survival (OS), with 100% OS in the HSCT group and 96% OS in the non-HSCT group (p = not significant).

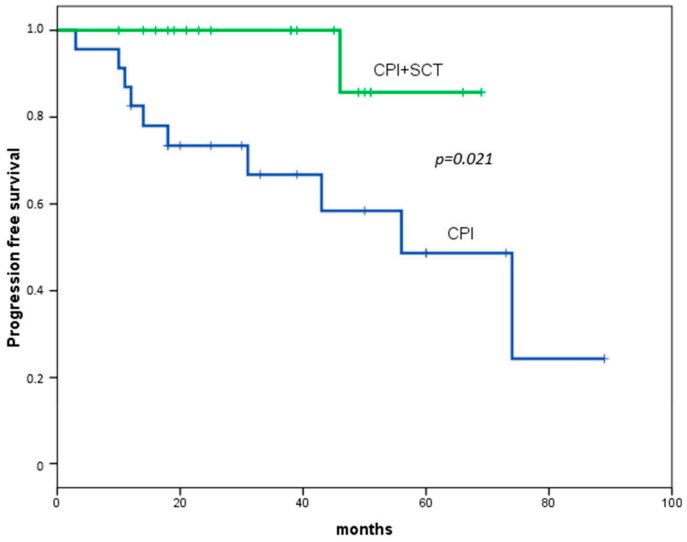

Figure 2. Progression-free survival in 42 patients with R/R cHL treated with PD-1 blockade who had or had not undergone HSCT.

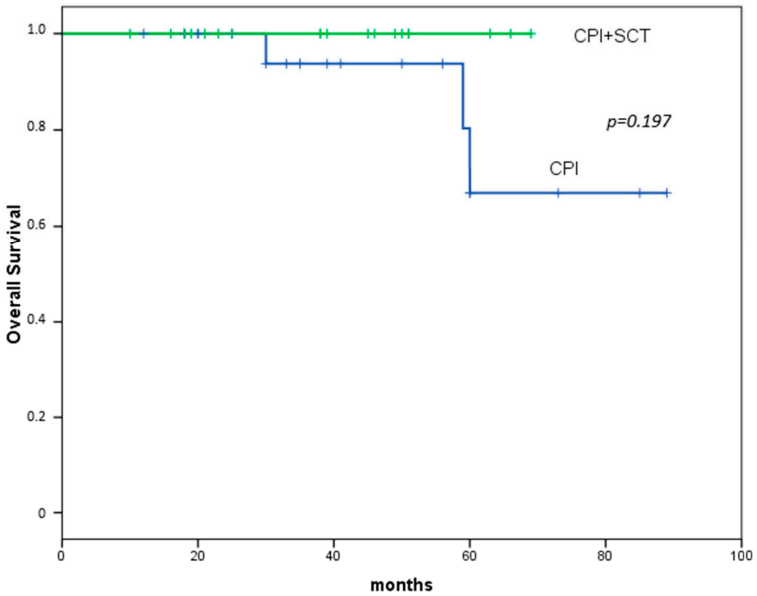

Figure 3. Overall survival in 42 patients with R/R cHL treated with PD-1 blockade who had or had not undergone HSCT.

Among the 15 patients in the non-HSCT group who received PD-1 inhibitors, seven were treated with nivolumab and eight with pembrolizumab. No significant differences were found between the two therapies in terms of PFS and OS. The 3-year PFS was 85% for nivolumab and 80% for pembrolizumab (p = 0.321), and the 3-year OS was 98% for nivolumab and 96% for pembrolizumab (p = 0.672).

At a median follow-up of 40 months, 31 patients (74%) remained alive and in CR, while 3 patients (7%) had died, 2 due to disease progression and 1 due to sepsis (see Table 3).

Table 3. Outcome After CPI Treatment.

Outcome	HSCT (*n* = 19)	No HSCT (*n* = 23)	*p*
Total	19	23	-
Relapse/progression after CPI (%)	1 (5%)	10 (43%)	0.005
Disease status at last follow-up:			
Alive in CR (%)	16 (84%)	15 (65%)	0.323
Died (%)	0 (0%)	3 (13%)	0.102
Cause of death:			
Infection (%)	1 (4%)	-	-
Hodgkin lymphoma (%)	2 (9%)	-	-

Abbreviations: CPI = checkpoint inhibitors; HSCT = hematopoietic stem cell transplantation.

Among the 31 patients in CR, 16 (7 from the HSCT group and 9 from the non-HSCT group) discontinued PD-1 therapy without showing signs of disease progression. The remaining 11 patients required further treatment: 7 continued with the same PD-1 inhibitor, 2 were treated with a combination of brentuximab vedotin and bendamustine, and 4 enrolled in a clinical trial with AZD7789, a bispecific anti-PD-1 and anti-TIM-3 antibody.

In terms of immune-related adverse events (irAEs), six patients in the HSCT group and four in the non-HSCT group experienced these events due to PD-1 therapy. The most common irAEs in both groups were rash (n = 5), fatigue (n = 4), and colitis (n = 3). Two patients in the HSCT group developed grade 2 colitis, which was managed with immunosuppressive therapy. Additionally, one patient in the non-HSCT group developed grade 3 pneumonitis, leading to discontinuation of PD-1 therapy and treatment with corticosteroids. Fortunately, no patient in either group experienced life-threatening irAEs requiring long-term immunosuppression or treatment beyond the management of the adverse event.

4. Discussion

Checkpoint inhibitors (CPIs) are transforming the standard of care for multiple cancer subtypes, leading to improved outcomes and long-term survival for a large subgroup of hematologic patients. In particular, PD-1/PD-L1 inhibitors have demonstrated good efficacy and a favorable toxicity profile in heavily pretreated classical Hodgkin lymphoma (cHL), with nearly 70% of patients responding, including those who had previously undergone hematopoietic stem cell transplantation (HSCT) and/or brentuximab vedotin (BV) therapy. Despite these promising results, a significant proportion of responding patients experience relapses, with a median progression-free survival (PFS) of 12 months [2,15,16,18,21,22].

This study presents a retrospective, multicenter analysis of 42 patients with relapsed/refractory cHL (R/R cHL) who responded to PD-1 blockade: 15 in partial remission (PR) and 27 in complete remission (CR). Our goal was to assess the different real-life treatment strategies employed within the Apulian hematology network. Although patients in the HSCT group were younger, and the non-transplanted group exhibited a higher number of complete remissions, baseline characteristics were otherwise comparable between the two groups. Notably, the relapse rate was significantly lower in the transplanted group than in the non-transplanted group (5% vs. 43%, p = 0.005) for both CR and PR patients. This highlights the continued importance of allogeneic HSCT in patients who relapse

after autologous HSCT, as it remains the only current treatment approach with curative potential [23].

Although the indications for allo-HSCT have remained largely unchanged in recent years, there is evidence of a progressive decrease in the total number of allogeneic transplants performed in patients with cHL [24,25]. A retrospective study by Merryman et al. suggested that patients undergoing allo-HSCT after nivolumab may experience a lower relapse rate than historical controls, although this strategy has not been directly compared with anti-PD-1 treatment without subsequent allo-HSCT [26]. In the Checkmate 205 study, 44 out of 243 patients proceeded to allo-HSCT, with a median follow-up of 5.5 months post-transplant. The 6-month cumulative incidence of treatment-related mortality (TRM) and disease progression was 13% and 7%, respectively [7,16].

Despite the prolonged duration of response observed with CPI treatment, relapses remain common, and allo-HSCT remains the only potentially curative treatment in R/R cHL patients, benefiting from the graft-versus-lymphoma effect [27,28]. Early reports following the introduction of CPIs as a bridge to allo-HSCT raised concerns about an increased risk of fatal acute graft-versus-host disease (GVHD) [29]. The effect of CPIs on T-cell activation and their long half-life may affect post-alloHSCT outcomes, potentially increasing non-relapse mortality. In our study, we observed an incidence of GVHD similar to previous reports from the pre-CPI era. Therefore, allo-HSCT may still be considered for patients with R/R cHL treated with PD-1 blockade, particularly in those who do not achieve a CR. However, when evaluating the risk/benefit ratio, the lack of overall survival (OS) benefit and the possibility of inducing a response with salvage chemotherapy following anti-PD1 "resensitization" should be considered.

An important clinical decision is whether to discontinue CPI treatment upon achieving a response or to continue until disease progression. In our series, patients who completed treatment were those in CR. One relapse was documented in the HSCT group (after auto-HSCT), and three relapses occurred in the non-HSCT group. Emerging data indicate that PD-1 blockade may "resensitize" cHL to standard chemotherapy, with patients who relapse or progress after anti-PD-1 therapy responding to salvage chemotherapy, even if previously refractory [22]. This approach has allowed some patients to receive consolidation with HSCT, increasing the likelihood of recovery [24].

In our analysis, 11 patients who were not candidates for auto-HSCT due to primary refractory disease achieved CR after CPI treatment and subsequently underwent auto-HSCT. In this group, only one patient relapsed. Interestingly, 8 out of 10 patients in PR at the time of transplantation converted to CR after HSCT. No significant difference in OS was observed between the transplanted and non-transplanted groups. Whether the observed PFS benefit translates into improved OS remains uncertain and should be re-evaluated with longer follow-ups. Further studies are needed to understand the biological rationale for the observed chemosensitization after CPI and to establish the most appropriate chemotherapy regimen and optimal timing of chemotherapy and PD-1 blockade in the therapeutic algorithm for R/R cHL.

There is growing evidence that retreatment with immunotherapy at disease progression may lead to a second, potentially long-lasting response. In the KEYNOTE-087 study, 11 out of 16 patients (69%) who discontinued therapy after achieving CR were able to achieve an objective response when rechallenged with pembrolizumab at relapse, with five patients (31%) achieving a second CR. In our study, three patients were retreated with a PD-1 blockade, achieving CR in two cases and stable disease (SD) in one. This phenomenon warrants further investigation, particularly as these therapies are administered early in the treatment sequence. Evaluating the potential influence of interval therapy on the outcomes of retreatment with PD-1 inhibitors remains an important question.

In addition, new targeted therapies, including antibody–drug conjugates and transcriptional agents, as well as combination therapies with CPI inhibitors or therapies targeting chimeric T-cell receptor antigens, are under investigation. Patients who do not respond to CPI should be considered for these alternatives to allogeneic transplants [25,26].

Our study has limitations, including the heterogeneity of the patient groups, the higher CR rate in the non-HSCT group, the younger population in the HSCT group, and the variability in prior therapies, including HSCT. Despite these limitations, this study provides valuable insights into the real-life therapeutic strategies used in the Apulian hematology network. This information can be useful for discussions with patients affected by R/R cHL to help guide the selection of the best treatment strategy.

5. Conclusions

In this study, we observed that a significant proportion of patients with relapsed/refractory classical Hodgkin lymphoma (R/R cHL) treated with PD-1 blockade, particularly those who did not achieve complete remission (CR), experienced disease progression. However, patients who responded to PD-1 blockade and subsequently underwent hematopoietic stem cell transplantation (HSCT) showed prolonged progression-free survival (PFS) compared with those who did not undergo transplantation, although this benefit did not translate into an overall survival (OS) advantage.

Our findings underscore the continued role of HSCT in patients with R/R cHL, particularly for those who do not achieve CR with PD-1 blockade therapy. However, the lack of a demonstrated OS benefit, combined with the potential for response to salvage chemotherapy following PD-1 "resensitization", should be carefully considered when evaluating the risk/benefit ratio of HSCT after checkpoint inhibitor treatment.

Furthermore, while retreatment with PD-1 inhibitors after relapse shows promising outcomes, further research is needed to optimize the use of CPi therapies in combination with other approaches, including novel agents and targeted therapies, to improve long-term outcomes for patients with R/R cHL [30,31].

In conclusion, while PD-1 blockade represents a significant advancement in the treatment of R/R cHL, more data and longer follow-ups are required to better define the role of HSCT and other therapeutic options in this context. The increasing availability of new treatments will further complicate therapeutic decisions but also offer hope for improved outcomes in this patient population.

Author Contributions: A.G., P.M. (Pellegrino Musto) and F.G. conceived and designed the study; P.M. (Pierluigi Masciopinto), V.B., D.P., N.D.R., V.P., A.M.C. and F.G. acquired the data; F.E.L. and F.G. drafted the manuscript. All authors revised the manuscript. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement: This study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study since the study data were collected during routine clinical activity and fully anonymized, and a formal institutional review board approval was exempted.

Informed Consent Statement: Each patient enrolled in this study was informed about the procedures and signed consent to allow data collection and analysis for research purposes.

Data Availability Statement: The data used for this research are available upon request to the corresponding author.

Conflicts of Interest: The authors declare no conflicts of interest.

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