Biol Blood Marrow Transplant 26 (2020) 1534–1542

Biology of Blood and Marrow Transplantation

journal homepage: www.bbmt.org

Analysis

Potential Survival Benefit for Patients Receiving Allogeneic Hematopoietic Stem Cell Transplantation after Nivolumab Therapy for Relapse/Refractory Hodgkin Lymphoma: Real-Life Experience in Spain

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Article history:
Received 4 November 2019
Accepted 3 February 2020

Keywords:
Hodgkin lymphoma
Nivolumab
Allogeneic transplantation
Relapsed/refractory lymphoma

A B S T R A C T

Clinical trials have shown that nivolumab has remarkable activity against relapsed/refractory classical Hodgkin lymphoma (cHL). However, the role of allogeneic hematopoietic stem cell transplantation (allo-HSCT) as consolidation therapy in these patients remains controversial. We performed a retrospective analysis of data from 74 patients treated with nivolumab. The overall response rate was 58% (including 30.6% with complete responses). Treatment-related adverse events were reported in 56.8% of patients (grade ≥3 in 9.4%). The main reasons for nivolumab discontinuation were referral for transplantation (41.7% patients) and disease progression (37.5%). The 2-year overall survival (OS) rate was 52% for the entire series. Ultimately, 39 patients underwent allo-HSCT. The cumulative incidence of grade II-IV acute graft-versus-host disease was 33.3% (grade III-IV in 2 patients). The cumulative incidence of nonrelapse mortality was 13.2%. Among the patients who responded to nivolumab, the 2-year OS and progression-free survival (PFS) were higher in patients who underwent consolidation with allo-HSCT (77.5% versus 42.6% [P = .126] and 73.9% versus 27.2% [P = .025], respectively). Thus, the efficacy and safety of nivolumab were comparable to values reported in previous clinical trials. The percentage of patients who bridged to transplantation was high, indicating a preference for Spanish physicians. These results suggest that consolidation allo-HSCT increases OS and PFS.

INTRODUCTION

Most patients suffering from classical Hodgkin's lymphoma (cHL) can be treated successfully with standard chemotherapy and/or radiotherapy, with 70% of them still alive at 10 years after diagnosis. The gold standard treatment for patients who fail first-line treatment is high-dose chemotherapy followed by

Financial disclosure: See Acknowledgments on page 1541.
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https://doi.org/10.1016/j.bbmt.2020.02.003
1083-8791/

autologous hematopoietic stem cell transplantation (auto-HSCT) [1-4]. Patients who fail auto-HSCT (or at least 2 previous lines of therapy) may be treated with brentuximab vedotin (Bv); however, in many patients, the disease will progress, with a median overall survival (OS) of approximately 22 months [5].

Nivolumab and pembrolizumab are immune checkpoint inhibitors that have been tested in patients with relapsed/refractory (R/R) cHL and have demonstrated remarkable anticancer activity and an acceptable safety profile [6-9]. Both drugs are currently approved by the US Food and Drug Administration and by the European Medicines Agency (EMA) for treatment of adults with cHL who have failed standard treatment approaches, including auto-HSCT and Bv therapy, and those who have failed 3 or more previous lines of systemic therapy. A recently published extended analysis of the nivolumab CheckMate 205 trial reported durable responses not only in patients showing complete remission (CR) or partial remission (PR), but also in those achieving stable disease, with similar 1-year OS rates [8]. However, 105 of 276 patients enrolled in the trial eventually experienced disease progression.

Although these new drugs seem to prolong median survival following auto-HSCT failure, their ability to cure patients with cHL is unknown. Thus, a notable proportion of patients are still considered candidates for a second transplantation, usually an allogeneic HSCT (allo-HSCT) subsequent to a reduced-intensity conditioning regimen. However, the role of nivolumab as a bridge to allo-HSCT is controversial owing to the potential increased risk of post-transplantation immune-related adverse events (AEs), such as severe acute graft-versus-host disease (GVHD) [10-12].

After the impressive results of the nivolumab phase I study, a significant number of cHL patients in Spain were granted early access to nivolumab through a Named Patient Program or compassionate use rules before EMA approval. The objective of this retrospective study was to examine the efficacy and safety profile of nivolumab for treatment of patients with R/R cHL in a real-life context.

METHODS

Study Design

This retrospective, multicenter, noninterventional study of nivolumab use in patients with R/R cHL included the participation of 34 centers from GELTAMO (Grupo Español de Linfoma y Trasplante de Médula Ósea). Eligible patients included patients with R/R cHL aged ≥18 years and treated with at least 1 cycle of nivolumab between September 2015 and May 2018. Patients were treated before market availability of the drug in Spain via a Named Patient Program or compassionate use rules. The decision to use nivolumab was made by the attending physician on an individual basis. All consecutive patients treated with nivolumab at GELTAMO participating centers were included in the study. Individual data were collected retrospectively by chart review at each center and reported to GELTAMO specifically for this study. The protocol was approved by the GELTAMO Institutional Review Board and by an independent reference Ethics Committee.

The primary endpoint was overall response rate (ORR). Secondary objectives were the CR rate, safety, and clinical outcomes for patients submitted (or not) for subsequent auto- or allo-HSCT.

Study Assessments

Lymphoma response assessment was based on local positron emission tomography (PET)/computed tomography (CT) scan results and on previously published recommendations and response criteria [13,14]. Patients with confirmed progressive disease (PD) according to clinical data but without imaging tests (PET/CT or CT) were also considered for response evaluation. Timing of response evaluation was established according to the local policies. Safety and tolerability were evaluated by recording the incidence, severity, and type of any AE according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 4.0.

Statistical Analysis

Data are presented as descriptive values and percentages or as median values and ranges, as appropriate. Investigators were asked to record the maximum response achieved at any time during treatment with nivolumab. The ORR was defined as the sum of the CR and PR rates. OS was defined as the time from the first dose of nivolumab, or the time of HSCT, to death due to any cause and was censored at the date of last available follow-up. Progression-free survival (PFS) was calculated only for those patients who proceeded to allo-HSCT and was defined as the time from transplantation to the time of death from any cause or as time to cHL progression. Actuarial survival analysis for OS and PFS was performed using the Kaplan-Meier method. All data were analyzed using SPSS for Windows, version 18.0 (SPSS, Chicago, IL).

RESULTS

Patient Characteristics

Seventy-four patients were included in the study; their demographic and baseline clinical characteristics are summarized in the Table 1. The median number of therapy lines before nivolumab was 4 (range, 1 to 15). Thirty-eight patients (51.4%) had undergone previous HSCT (auto-HSCT, n = 33 [44.6%]; allo-HSCT, n = 5 [6.8%]). Almost all the patients (97.3%) were treated with Bv before nivolumab. At the time of nivolumab initiation, most patients (70.3%) had advanced disease (stage III-IV), 41.9% B-symptoms, 17.6% bulky disease, and 66.2% extranodal involvement.

Treatment with Nivolumab and Safety

All patients received nivolumab monotherapy at a dose of 3 mg/kg (n = 69; 93.2%) or 4 mg/kg (n = 1; 1.4%) once every 2 weeks (dose unknown, n = 4). The median number of nivolumab cycles was 8 (range, 1 to 89; interquartile range, 6 to 14). Most patients (n = 53, 72%) received treatment for ≤6 months. At the time of this report, 2 patients (2.7%) were still being treated. The reasons for nivolumab discontinuation were referral for HSCT in 30 patients (41.7%), cHL progression in 27 (37.5%), nivolumab AEs in 8 (11.1%), achievement of maximum response or 2 years of treatment in 4 (5.6%), patient or physician's decision in 2 (2.8%), and unknown in 1 (1%). A total of 79

Table 1
Patient Characteristics at Nivolumab Initiation (N = 74)

Characteristic	Value
Age, yr, median (range)	32 (17-78)
Sex, n (%)	
Male	46 (62.2)
Female	28 (37.8)
cHL histology subtype, n (%)	
Nodular sclerosis	50 (67.6)
Mixed cellularity	16 (21.6)
Lymphocyte-rich	4 (5.4)
Lymphocyte-depleted	1 (1.4)
Unknown	3 (4)
Number of previous therapy lines, median (range)	4 (1-15)
cHL refractory to first-line therapy, n (%)	40 (54.1)
Auto-HSCT before nivolumab, n (%)	33 (44.6)
Allo-HSCT before nivolumab, n (%)	5 (6.8)
Bv before nivolumab, n (%)	72 (97.3)
Time from HL diagnosis to first dose of nivolumab, yr, median (range)	2 (.5-18.5)
Ann Arbor stage at nivolumab initiation, n (%)	
I	3 (4.1)
II	19 (25.7)
III	9 (12.2)
IV	43 (58.1)
B-symptoms at nivolumab initiation, n (%)	31 (41.9)
Bulky disease at nivolumab initiation, n (%)	13 (18.3)
Extranodal disease at nivolumab initiation, n (%)	49 (67.1)

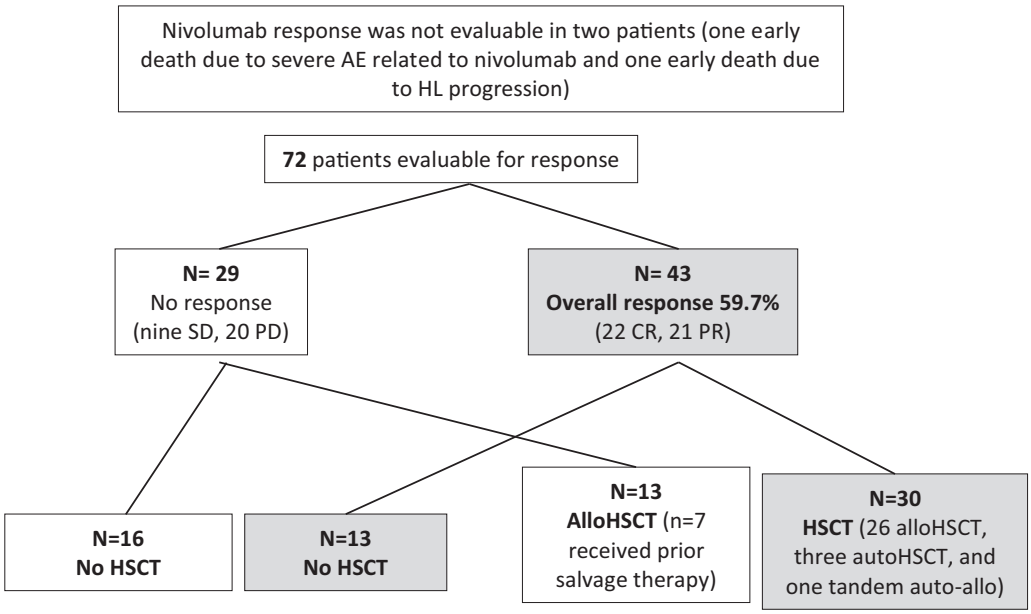

Figure 1. Efficacy of nivolumab: disposition of patients.

AEs were reported in 42 patients (56.8%). The most common (>5%) AEs of any grade were infection (20.3%), hepatitis (9.5%), diarrhea (9.5%), rash/erythema (9.5%), neutropenia (8%), anemia (6.7%), fever (6.7%), and hypothyroidism (5.4%). Twenty-four AEs (32.4%) were reported as "probably immune-related": 20.3% were grade 1-2 (cutaneous, n = 5; hepatitis, n = 3; hypothyroidism, n = 3; gastrointestinal, n = 3; suprarenal insufficiency, n = 1); 6.3% were grade 3-4 (pneumonitis, n = 2; hepatitis, n = 1; encephalitis, n = 1; hypothyroidism, n = 1); and 5.1% were grade 5 (pneumonitis, n = 1; Stevens–Johnson syndrome, n = 1; hepatitis, n = 1; nephritis, n = 1). Two patients died due to severe AEs secondary to nivolumab. The first patient was heavily pretreated, having undergone 2 allo-HSCTs (the last one 3 years before nivolumab initiation). After the first dose of nivolumab, the patient developed grade 5 hepatitis, nephritis, and Steven-Johnson syndrome, leading to death.

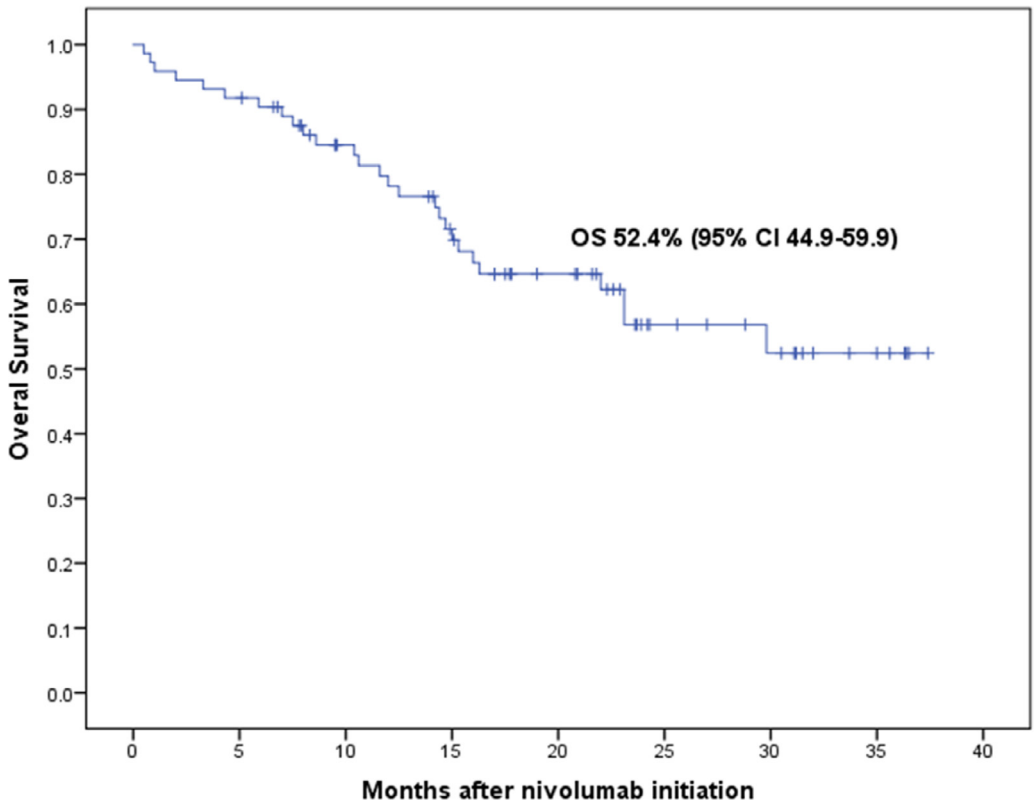

Figure 2. OS of all patients (n = 72) after nivolumab treatment.

The second patient received nivolumab after 4 previous lines of therapy and died due to grade 5 pneumonitis after 2 cycles of nivolumab.

Efficacy

The response to nivolumab was evaluable in 72 patients (Figure 1). The median time to best response (CR/PR/stable disease [SD]) was 3 months (range, .5 to 13.5 months). Most patients achieved CR or PR within the first 6 months of treatment; only 2 responses were observed after that, 1 CR at 12 months and 1 PR at 13.5 months. The ORR was 59.7%, including CR in 22 patients (30.6%) and PR in 21 patients (29.1%). Nine patients (12.5%) achieved SD, and 20 (27.8%) showed progression of lymphoma. Seven patients developed disease progression after initially achieving PR (n = 4) or SD (n = 3). Six of the 72 evaluable patients (8.3%) were alive and showing a response to nivolumab without additional treatment. The median follow-up for survivors from the time of nivolumab initiation was 22 months (range, 6.8 to 42.8 months). The estimated probability of 2-year OS was 52% (95% confidence interval [CI], 44.9% to 59.9%) (Figure 2).

A small group of patients (n = 5) received nivolumab after a previous allo-HSCT; the median time from transplantation to first dose of nivolumab was 58 months (range, 40 to 84 months). The median number of nivolumab cycles was 5 (range, 1 to 18). The maximum response to nivolumab was as follows: 4 patients achieved PR (1 patient was not evaluable due to early death), and 3 eventually died due to HL progression. Two grade ≥4 AEs were observed, both after a single dose of nivolumab; 1 patient had grade 4 encephalitis, and another died due to Steven-Johnson syndrome plus hepatitis and nephritis. Finally, 1 patient developed grade 3 pneumonitis after 14 cycles of nivolumab.

Patients who did not proceed to HSCT (auto- or allo-; n = 29) received a median 12 cycles of nivolumab (range, 1 to 89); 2 remained under treatment at the time of this report. Five patients (17.2%) achieved CR, 8 (27.6%) achieved PR, 3 (10.3%) achieved SD, and 13 (44.8%) showed progression of lymphoma. All but 1 patient eventually showed disease progression. Sixteen patients died due to HL progression (n = 12), infection (n = 3), and a car accident (n = 1). Disease status at the last follow-up was CR in 8 patients, PR in 3 patients, SD in 1 patient, and PD in 17 patients (1 unknown). After a median follow-up of 17.5 months (range, 5.1 to 32 months) for surviving patients, 2-year OS and PFS were 21% and 18%, respectively.

Outcomes for Patients Treated with Nivolumab Who Proceeded to HSCT

Forty-two of 72 patients (58.3%) proceeded to HSCT (3 to auto-HSCT, 38 to allo-HSCT, and 1 to tandem auto-allo-HSCT) (Figure 1). All 3 patients who underwent auto-HSCT achieved CR after nivolumab and showed a sustained CR at 12, 14, and 19 months of follow-up post-transplantation.

Thirty-nine patients proceeded to allo-HSCT after a median of 8 (range, 4 to 44) nivolumab doses. The median time from the last dose of nivolumab to allo-HSCT was 1.9 months (range, .5 to 5.7 months). Sixteen patients (41%) underwent previous auto-HSCT, all of whom had been treated with Bv. Ten patients (25.6%) received additional therapy between the last dose of nivolumab and allo-HSCT, including 4 with gemcitabine plus oxaliplatin, 3 with radiotherapy, 2 with Bv plus bendamustine, and 1 with auto-HSCT as part of a tandem auto-allo-HSCT schedule. The characteristics of the allo-HSCTs are summarized in Table 2.

Table 2
Characteristics of Allo-HSCTs (N = 39)

Characteristic	Value
Disease status at transplantation, n (%)	
CR	25 (64.1)
PR	5 (12.8)
Stable disease	3 (7.7)
Refractory disease	5 (12.8)
Unknown	1 (2.6)
Type of donor, n (%)	
HLA-identical sibling	15 (38.5)
HLA-identical unrelated	3 (7.7)
Haploidentical	20 (51.3)
Unknown	1 (2.6)
Stem cell source, n (%)	
Peripheral blood	37 (95)
Bone marrow	2 (5)
Intensity of conditioning regimen, n (%)	
Myeloablative	1 (2.6)
Reduced conditioning	35 (89.7)
Unknown	3 (7.7)
Type of conditioning regimen, n (%)	
Fludarabine + busulfan + cyclophosphamide	15 (38.5)
Fludarabine + melphalan	8 (20.5)
Fludarabine + busulfan + thiotepa	6 (15.4)
Fludarabine + busulfan	3 (7.7)
Fludarabine + cyclophosphamide + total body irradiation	3 (7.7)
Busulfan	1 (2.6)
Unknown	3 (7.7)
GVHD prophylaxis, n (%)	
Post-transplantation cyclophosphamide-based	
Using a haploidentical donor	17 (43.6)
Using an HLA-identical sibling donor	3 (7.7)
Calcineurin-based (1 case plus antithymocyte globulin)	16 (41.0)
Unknown	3 (7.7)

The 1-year cumulative incidence of nonrelapse mortality was 13.2%. All deaths occurred within the first 6 months after allo-HSCT; 1 patient who underwent transplantation at 26 days after the last dose of nivolumab died from grade IV steroid-refractory acute GVHD, 2 patients died from infection, 1 patient died due to hepatic veno-occlusive disease (VOD), and 1 patient died from interstitial pneumonia. In addition, 3 patients died due to HL progression at 6.7, 7.9, and 18 months post-transplant. Fourteen (35.9%) patients developed steroid-requiring non-infectious febrile syndrome and three developed hepatic VOD. The cumulative incidence of grade II–IV acute GVHD was 33.3% (only two patients developed grade III–IV GVHD), and the cumulative incidence of chronic GVHD was 35.3%.

The median follow-up for survivors from alloHSCT was 18.4 months (4.2–45.7). Median post-transplant PFS and OS was not reached, with a 2 year estimated PFS and OS of 69.4% and 71.9%, respectively (Figure 3). Univariate analysis of variables that could influence OS and PFS such as age, sex, number of therapy lines before nivolumab, autoHSCT before nivolumab, additional therapy between nivolumab and alloHSCT, and time from last dose of nivolumab to alloHSCT did not show any statistical differences. Disease status at transplantation (CR/PR versus SD/PD) was associated with better outcomes although differences were not statistically significant (2-year OS, 75% versus 57%, P = .368; 2-year PFS, 72% versus 57%; P = .439). In

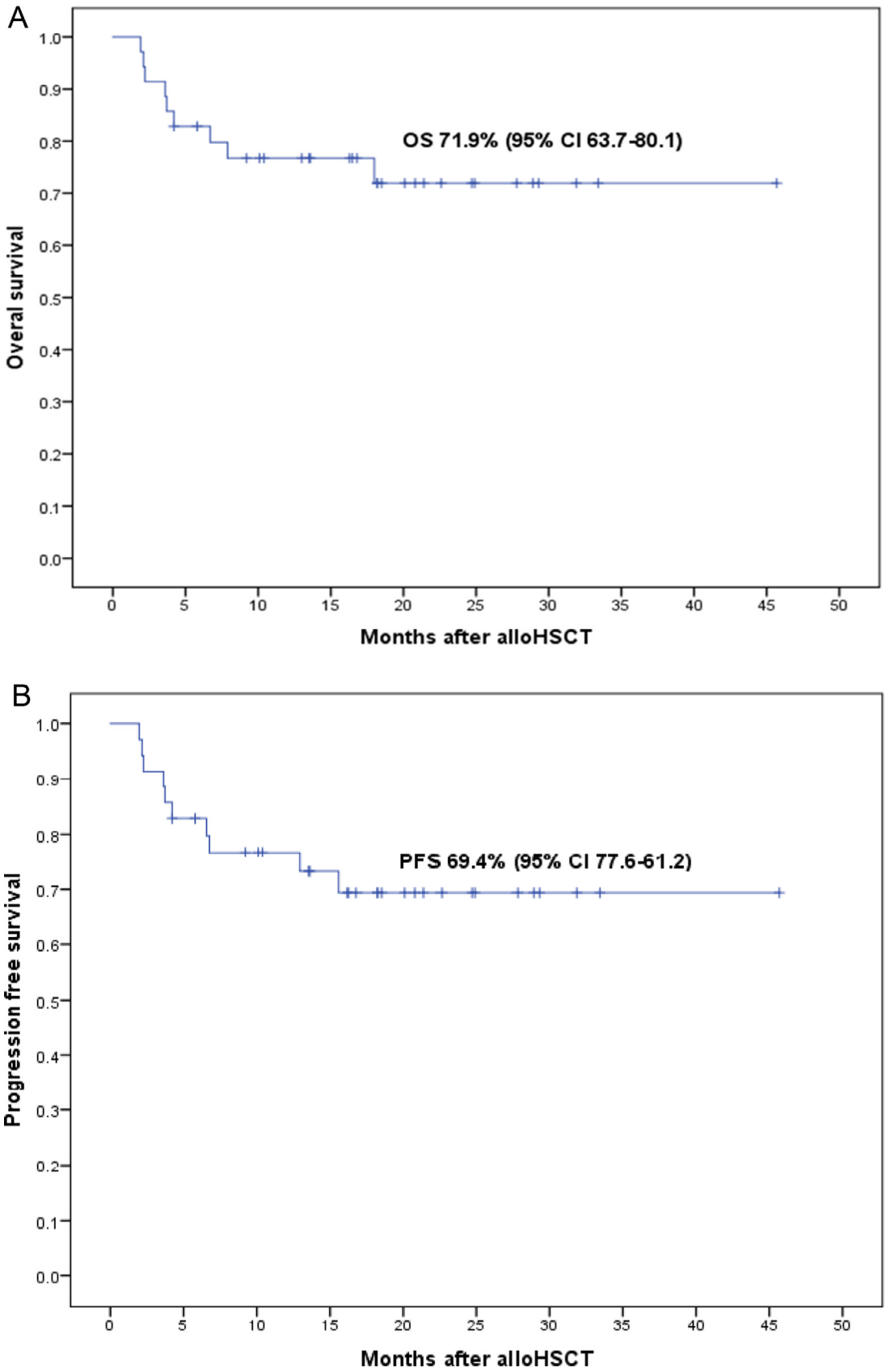

Figure 3. OS (A) and PFS (B) of patients undergoing allo-HSCT after nivolumab treatment.

addition, there was a trend for better survival with the use of HLA-identical sibling donors compared with haploidentical or unrelated donor (2-year OS, 92% versus 66%, P = .075; 2-year PFS, 83% versus 59%, P = .169).

To assess whether patients responding to nivolumab benefit from allo-HSCT as consolidation therapy, we performed a comparison analysis of allo-HSCT (n = 27) versus no-alloHSCT (n = 13) restricted to patients achieving CR/PR after nivolumab. Characteristics and outcomes of these patients are summarized in Table 3. At nivolumab initiation, patients in the allo-HSCT group were younger and the number of cases with extranodal lymphoma was lower. No between-group differences were observed in HL stage, B symptoms, or primary refractory disease. The number of previous therapy lines was lower in the allo-HSCT group, including less auto- or allo-HSCT. As expected, patients who underwent allo-HSCT received lower number of nivolumab cycles (median, 7 versus 16; P= .009). No significant between-group differences were seen in the median time to response from nivolumab initiation (3 versus 3.5; P = .2) or in the proportion of patients achieving CR (51.9% versus 38.5%; P = .427). The estimated probability of 2-year OS was 77.5% (median not reached) for allo-HSCT recipients and 46.2% (median, 21.7 [95% CI, 18.9 to 37.3] months) for the nontransplantation group (P = .126). The estimated probability of 2-year PFS was 73.9% (median not reached) for the transplantation group versus 27.2% (median, 20.6 [95% CI, 9.9 to 31.2] months) for the nontransplantation group (P = .025).

DISCUSSION

This retrospective multicenter study analyzed real-life data regarding nivolumab use in patients with R/R cHL in Spain. The results show that the ORR was similar to that reported previously in clinical trials, and suggests that allo-HSCT after nivolumab increases OS and PFS.

In addition to data from the phase II CheckMate 205 clinical trial [8], 4 large studies have published real-world results of nivolumab use in patients with R/R cHL [15-18]. These results are summarized in Table 4. In these studies, ORR and CR rates were 64% to 69% and 15% to 45%, respectively, comparable to the response rates reported in the present study (ORR, 59.7%; CR, 30.6%).

The most common AEs of any grade in our cohort were infection, hepatitis, diarrhea, rash/erythema, neutropenia, anemia, fever, and hypothyroidism. A recent meta-analysis of the results of prospective clinical trials of an anti-PD-1 monoclonal antibody in 718 patients with lymphoma (604 with cHL) reported that the most common AEs of any grade were fatigue, rash, hypothyroidism, thrombocytopenia, and pyrexia, and that the most common grade ≥3 AEs were neutropenia, pneumonitis, rash, and leukopenia, all with an incidence of <5% [19]. Only 2 drug-related deaths were reported in this meta-analysis. In the context of real-life reports, the percentage of grade ≥3 AEs seems to be higher than that reported in clinical trials. Manson et al [17] reported that 37% of patients sustained grade ≥3 AEs, and 20.5% had severe AEs. Berköz et al [15]

Table 3
Characteristics and Outcomes of Patients in CR/PR after Nivolumab According to Subsequent Allo-HSCT

Characteristic at Nivolumab Initiation	Allo-HSCT (N = 27)	No Allo-HSCT (N = 13)	*P* Value
Age, yr, median (range)	32 (17-49)	41 (26-78)	**<.0001**
Sex, n (%)			
Male	18 (66.7)	4 (30.8)	
Female	9 (33.3)	9 (69.2)	.871
Stage disease III-IV, n (%)	17 (62.9)	12 (92.3)	.109
Bulky disease, n (%)	8 (32)	0	**.027**
Extranodal disease, n (%)	13 (48.1)	12 (92.3)	**.007**
B symptoms, n (%)	13 (48.1)	8 (61.5)	.666
Previous lines of systemic therapy, median (range)	4 (3-6)	6 (2-15)	**.002**
Refractory to first-line therapy, n (%)	12 (44.4)	8 (61.5)	.311
Previous Bv, n (%)	27 (100)	13 (100)	–
Previous auto-HSCT, n (%)	11 (40.7)	10 (76.9)	**.032**
Previous allo-HSCT, n (%)	0	4 (30.8)	**.002**
Cycles of nivolumab, median (range)	7 (4-44)	16 (1-89)	**.009**
Reason for treatment discontinuation, n (%)	N = 27	N = 12	–
HL progression	1 (3.7)	5 (41.7)	
Toxicity	2 (7.4)	3 (25)	
Obtention of maximum response	0	2 (16.7)	
End of treatment (2 yr)	0	1 (8.3)	
Consolidation with allo-HSCT	22 (81.5)	0	
Other	2 (7.4)	1 (8.3)	
Best overall response, n (%)			
CR	14 (51.9)	5 (38.5)	
PR	13 (48.1)	8 (61.5)	.427
Time to best response to nivolumab, mo, median (range)	3 (1.5-12)	3.5 (.5-13.5)	.2
Relapse/progression, n (%)	3 (11.1)	5 (38.5)	**.045**
Death, n (%)	5 (18.5)	5 (38.5)	.195
OS, %	77.5	46.2	.126
PFS, %	73.9	27.2	**.025**

Table 4
Results of the CheckMate 205 Trial and the Real-Life Series of Patients with HL Treated with Nivolumab

Series	No.	Bv Pre-Nivolumab, %	Auto-HSCT Pre-Nivolumab, %	Allo-HSCT Pre-Nivolumab, %	Cycles of Nivolumab, median (range)	Reason for Stopping Nivolumab	ORR, % (CR)	Allo-HSCT Post-Nivolumab, n	Follow-Up, mo, median (range)	OS, %
GELTAMO; Martínez et al	74	97	45	7	8 (1-89)	HSCT, 42%; HL progression, 38%; toxicity, 11%; still under treatment, n = 2	60 (31)	39	22 (6.8-42.8)	52% at 2 yr; 74% at 2 yr for allo-HSCT recipients
LYSA; Manson et al1[7]	78	100	62	28	9.5 (1-84)	HSCT, n = 14; HL progression, n = 34; toxicity, n = 6; death, n = 2; other, n = 11; still under treatment, n = 11	66 (38)	17	34 (.1-40)	65% at 3 yr; 82% at 1 yr for allo-HSCT recipients
Turkish series; Beköz et al1[5]	82	77%	67	30	12 (1-40)	HSCT, n = 11; HL progression, n = 23; toxicity, n = 5; still under treatment, n = 41	64 (21)	11	7 (1-22)	91% at 6 mo
Italian series; Santoro et al1[6]	133	96%	55	20	10.6 (1-19)	HSCT, n = 31; HL progression, n = 21; toxicity, n = 14; other, n = 2	68 (15)	20	-–	89% at 1 yr
US series; Bair et al[18]	53	91%	53	19	-–	Auto-HSCT, n = 2; HL progression, n = 14; toxicity, n = 8; other, n = 10	68 (45)	1	20	89% at 1 yr
CheckMate 205 trial; Armand et al8	243	74%	100	0	30	HL progression, n = 62; toxicity, n = 19; other, n = 57; still under treatment, n = 97	69 (16)	44	18 (IQR, 15-22)	92% at 1 yr; 87% at 6 mo for allo-HSCT recipients

reported discontinuation of nivolumab in 4 patients due to a severe pulmonary AE (n = 1), autoimmune encephalitis (n = 1), and aggravation of GVHD (n = 2), resulting in 1 death. Bair et al [18] reported grade 3-4 AEs in 16% of allo-HSCT-naïve patients, including grade 4 encephalitis and pneumonitis. Here we observed a 11.4% rate of grade ≥3 AEs (pneumonitis, n = 3; hepatitis, n = 2; encephalitis, n = 1; hypothyroidism, n = 1; Stevens-Johnson syndrome, n = 1; and nephritis, n = 1), leading to 2 deaths. Although the results of these retrospective studies must be interpreted with caution, the data suggest that the real-world safety profile of nivolumab may differ from that observed in clinical trials, which do not enroll patients with a high risk of severe AEs (ie, those with a history of allo-HSCT or autoimmune disorders).

It is a matter of debate whether patients responding to nivolumab require allo-HSCT as consolidation therapy. Although the response rates to nivolumab observed herein were similar to those reported previously, it is noteworthy that the percentage of patients who bridged to allo-HSCT was higher in this study than in previous studies (54.2% versus 18% in the CheckMate 205 trial, 17% in the LYSA cohort, 11% in a Turkish cohort, and 20% in an Italian cohort) (Table 4) [8,15-17]. Limited information exists regarding the impact of nivolumab and other PD-1 inhibitors on transplantation outcomes. Initial reports suggest that allo-HSCT in this setting could be associated with increased risk of early transplantation-related toxicity, mainly acute GVHD and hepatic VOD [10-12]. Dada et al [20] conducted a pooled analysis to compare the safety of allo-HSCT in 2 cohorts of patients with R/R HL, 1 cohort with (n = 122) and the other without (n = 978) pretransplantation treatment with PD-1 inhibitors. The authors concluded that allo-HSCT after PD-1 inhibitors is feasible and not associated with higher mortality (15% in the pretreatment cohort versus 19% in the no pretreatment cohort). However, the incidence of severe acute GVHD was significantly higher in patients previously exposed to these drugs (28% versus 8%). Nonetheless, the heterogeneity of these retrospective data, particularly with respect to risk factors that influence the incidence and severity of GVHD, prevents the drawing of accurate conclusions. Here the incidence of grade II-IV acute GVHD was 33%, with only 2 patients developing grade III-IV GVHD; this may be due to the use of high-dose post-transplant cyclophosphamide as GVHD prophylaxis in a significant number of patients (51.3%). We observed affordable toxicity, with a cumulative incidence of non-relapse mortality of 13.2% at 1 year and no late deaths. In the present series, which had a longer post-transplantation follow-up than those published by Armand et al [8] and Merryman et al [10] (ie, median, 18.4 months versus 5.5 and 12 months, respectively), we observed a promising PFS and OS (69.4% and 71.9%, respectively). In contrast to the values reported by Manson et al [17], allo-HSCT recipients had better PFS and OS than patients who did not undergo subsequent transplantation (71.9% versus 21%). Our results show that this benefit of allo-HSCT on PFS persists even when the comparison between allo-HSCT and no transplantation is restricted to patients who achieved a CR/PR after nivolumab therapy (73.9% versus 27.2%; $P = .025$).

In our experience, almost all patients who do not undergo HSCT either relapse or progress, especially those who fail to achieve a CR after nivolumab therapy. Only 6 (8.3%) of all evaluable patients were alive and showing a response after nivolumab without any additional treatment. This finding is in agreement with Manson et al [17], who reported that a 62.2% relapse rate in their patients without subsequent transplantation. Clinical trials suggest that the vast majority of responses to nivolumab are partial, and that a gradual loss of response over time is common, even in patients with ongoing therapy. In the CheckMate 205 trial, patients achieving CR and PR showed a median response duration to nivolumab of 20.3 and 12.8 months, respectively [8]. In contrast, prolonged remission after PD-1 discontinuation was reported for some patients who achieved CR, some of them beyond 2 years [6,21]; whether some of these patients were cured is unclear.

Taken together, these results suggest that patients achieving PR after nivolumab should be referred for an allo-HSCT consultation, whereas the procedure could be deferred in those achieving CR. Of note, the present study was not intended to compare outcomes between patients who did or did not undergo consolidation with allo-HSCT. Our results simply reflect the current clinical practice in Spain, which is a general preference for nivolumab as a bridge to allo-HSCT. This represents a limitation of this study, because we cannot know what the outcome would have been for patients who responded to nivolumab but did not undergo subsequent allo-HSCT.

In conclusion, the safety and efficacy of nivolumab reported herein are comparable to the findings of previous studies. In our series, the main reasons for nivolumab discontinuation were referral for HSCT and disease progression. Based on a median follow-up of almost 2 years, these results demonstrate that consolidation with allo-HSCT is associated with favorable PFS and OS. Only a small proportion of patients who received nivolumab without additional treatment are alive. This study represents an opportunity to analyze and learn from the outcomes of real-world patients, who differ from the highly selected cohorts enrolled in clinical trials.

ACKNOWLEDGMENTS

We thank all the patients for their participation, and Cristina Fernández from GETLAMO for help with statistical analysis. We also thank the other investigators who participated in the study: Elena Amutio (Hospital Universitario de Cruces, Bilbao), Carmen Calle (Hospital General Universitario de Ciudad Real, Ciudad Real), Juana Clavel (Hospital General Universitario de Castellón, Castellón), Eva M. Donato (Hospital Universitario Doctor Peset, Valencia), Elena Fernández (Hospital Rio Hortega, Valladolid), Alfonso García de Coca (Hospital Universitario de Valladolid, Valladolid), Pilar Gómez-Prieto (Hospital La Paz, Madrid), M. Sonia González-Pérez (Hospital Clínico Universitario de Santiago, Santiago de Compostela), José A. Hernández-Rivas (Hospital Universitario Infanta Leonor, Madrid), Beatriz López-Pulido (Hospital de Jerez de la Frontera, Cádiz), M. Paz Martínez-Badás (Complejo Asistencial de Ávila, Ávila), Miriam Moreno (Hospital Germans Trias i Pujol, Badalona), Elena Rámila (Hospital Universitario Parc Taulí, Barcelona), Mercedes Varela (Hospital Universitario Lucus Augusti, Lugo), Lucía Villalón (Hospital Universitario Fundación de Alcorcón, Madrid), and M. Cruz Viguria (Complejo Hospitalario de Navarra, Pamplona).

Financial disclosure: This study was sponsored by the Spanish Group of Lymphoma and Bone Marrow Transplantation, GELTAMO. Bristol-Myers Squibb provided financial support for administrative local tasks at the participating hospitals.

Conflict of interest statement: There are no conflicts of interest to report.

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