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Nivolumab as a bridge to allogeneic hematopoietic stem cell transplantation is associated with improved survival

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Abstract. – OBJECTIVE: The aim of the present study was to compare the effects of nivolumab bridge to allogeneic hematopoietic stem cell transplantation (allo-SCT) on progression-free survival (PFS) and overall survival (OS) and toxicity profile.

PATIENTS AND METHODS: The study population consisted of relapsed/refractory cases of HL, who were treated with nivolumab for disease control and subsequently underwent allo-SCT at our institution. The control group consisted of HL patients who relapsed or refractory after multiple lines of therapy and underwent allo-SCT without nivolumab before transplantation as bridging therapy.

RESULTS: The incidence of acute and chronic graft *vs.* host disease (GVHD) was similar in both groups. The 100-day mortality occurred in 1 patient (10%) in the nivolumab group and 4 patients (16.7%) in the control group ($p = 0.54$). During 30-month follow-up, PFS was achieved in 60% of patients in the nivolumab group and 45.8% in the control group ($p = 0.69$). OS during 30-month follow-up was 80% in the nivolumab group and 41.7% in the control group, OS was superior in patients in the nivolumab group than in the control group ($p = 0.04$).

CONCLUSIONS: Allo-SCT after bridging therapy with nivolumab provides a survival advantage over patients who underwent allo-SCT without the bridging. Therapy with nivolumab in combination with post-transplant cyclophosphamide does not appear to increase GVHD.

Key Words:
Nivolumab, Hematopoietic stem cell transplantation, Hodgkin lymphoma.

Introduction

Programmed cell death protein 1 (PD-1) is expressed in CD4 and CD8 T cells and exerts an inhibitory effect on activated T cells[1]. PD -L1 and PD -L2 are the ligands of PD -1 and are expressed in various cell types, including hematopoietic cells[2,3]. Expression of PD -L1 and PD -L2 in tumor cells has been associated with poor prognosis. Since PD -L1 expression allows tumor cells to evade the immune system[4,5]. PD -1/ PD -L1 inhibitors are currently used to treat a number of cancers, including Hodgkin's lymphoma (HL)[6-8]. PD -1 inhibition exerts its anticancer effects *via* suppression of antitumor immune responses[8]. HL has been shown to be particularly susceptible to blockade of PD -1 signaling. Since a striking feature of HL is the high number of PD -L1-positive T cells in the tumor microenvironment[7].

Nivolumab was approved by the Food and Drug Administration (FDA) for the treatment of relapsed/refractory HL after initial data showed a favorable efficacy and safety profile. Based on previous randomized trials[8,9], the use of nivolumab is indicated in relapsed/refractory HL patients who have previously received autologous hematopoietic stem cell transplantation (auto-SCT) and brentuximab vedotin (BV) therapy. Indeed, the prognosis in this patient population is poor, with a median overall survival of 2 years[10]. In a recent single-arm multicohort phase 2 study of 243 patients with relapsed refractory HL[8], the objective response rate was 69% with a median follow-up of 18 months. Nivolumab has also been studied as a bridge to allogeneic hematopoietic stem cell transplantation (allo-SCT) in relapsed refractory patients with HL[11]. The results are promising, as bridging therapy with nivolumab does not appear to result in prohibitive immunotoxicity. In addition, graft *vs.* host disease (GVHD) did not increase in this group. However, the number of HL patients receiving nivolumab as a bridge to allo-SCT is relatively

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small. In addition, other groups have reported higher rates of severe GVHD in patients receiving nivolumab as a bridge to allo-SCT[12].

Many patients who received nivolumab for relapsed/refractory HL eventually relapse. Therefore, consolidation with allo-SCT may prolong overall survival (OS)[13]. In the present study, we aimed to analyze the safety and efficacy of nivolumab as a bridge to allo-SCT in patients with relapsed/refractory HL. We also compared the effects of using nivolumab as a bridge to allo-SCT on progression-free survival (PFS), OS, and toxicity profile.

Patients and Methods

Study Design, Setting and Participants

This is a retrospective, single-center study of relapsed or refractory HL patients treated at the Department of Hematology and Stem Cell Transplantation, Dr. Abdurrahman Yurtaslan Oncology Hospital. The present study was reviewed and approved by Non-Interventional Clinical Researches Ethics Committee of Dr. Abdurrahman Yurtaslan Oncology Hospital.

Patients in this study consented to participate in the study with the understanding that their data would be used anonymously.

The study population consisted of patients who had relapsed or were refractory to multiple lines of treatment HL. These patients were treated with nivolumab for disease control and subsequently underwent allo-SCT at our institution between June 2017 and June 2020. All patients were treated with auto-SCT and received BV prior to treatment with nivolumab. The conditioning regimen for auto-SCT in all patients was carmustine, etoposide, cytarabine, and melphalan. Patients who relapsed after auto-SCT or BV were candidates for nivolumab therapy as a bridge to allo-SCT. Patients at this stage received nivolumab at a dose of 3 mg/kg. The conditioning regimen for allogeneic allo-SCT in these patients consisted of fludarabine, antithymocyte globulin, total body irradiation at a dose of 8 or 12 Gy, and post-transplant cyclophosphamide (Flu- ATG-TBI + post Cy). During this period, 10 patients receiving nivolumab as bridging therapy were assigned to the study population. The control group consisted of HL patients who had undergone allo SCT between 2010 and 2017 without receiving nivolumab as bridging therapy prior to transplantation. Patients in the control group also relapsed or were refractory after multiple lines of therapy.

Data Collection

The following data were collected by reviewing patient records: age, sex, disease stage and type. Treatment history and response to treatment were reviewed for each patient. The efficacy and toxicity of nivolumab were evaluated by examining the presence of complications previously reported to be associated with nivolumab use[13]. The compatibility of donor stem cells and recipient human leukocyte antigens was examined. The occurrence of acute or chronic GVHD was also recorded. Acute GVHD was suspected if patients developed signs or symptoms related to the skin, liver, or gastrointestinal tract. The sign and symptoms include blisters, dermatitis, abdominal pain, diarrhea, persistent nausea, and hepatitis. Acute GVHD was graded as previously described[14]. Chronic GVHD was diagnosed according to National Institutes of Health criteria, which require at least one diagnostic sign and one characteristic sign and exclusion of other diagnoses[15].

Statistical Analysis

Statistical analysis was performed using Statistical Package for the Social Sciences (SPSS, Chicago, IL, USA) version 18. Student's *t*-test was performed to analyze parametric data with normal distribution. Chi-square test and linear association test were performed to analyze dichotomous and ordinal data. Kaplan-Meier survival analysis was used to describe PFS and OS in HL patients after allo-SCT. OS was defined as the time from allo-SCT to death from any cause. PFS was defined as the time from Allo-SCT to death from disease progression or any other cause. A p-value of less than 0.05 was considered statistically significant.

Results

The clinical and disease characteristics of the patients are shown in Table I. The mean age of patients who received nivolumab before allo-SCT (group 1) was 26.5 years, and the mean age of patients in the control group (group 2) was 34.7 years. There was no statistically significant difference between the groups in terms of age. The sex distribution of patients was similar in both groups, as was the distribution of HL subtypes. In both groups, the majority of cases were of the nodular sclerosing type (80% *vs.* 66.7% in groups 1 and 2, respectively, $p = 0.34$). Ann Arbor stages

Table I. Clinical and disease characteristics of patients and control group.

Patients	Group 1 (n: 10)	Group 2 (n: 24)	p
Age at diagnosis [mean (min-max)]	26.5 (19-42)	34.7 (17-55)	0.06
Gender n (%)			0.85
Female	3 (30 %)	8 (33.3 %)	
Male	7 (70 %)	16 (66.7 %)	
Hodgkin subtype n (%)			0.34
Lymphocyte rich HL	1 (20 %)	2 (8.3 %)	
Mixed cellularity HL	1 (10 %)	5 (20.8 %)	
Nodular sclerosis HL	8 (80 %)	16 (66.7 %)	
Lymphocyte depleted HL	0	1 (4.2 %)	
Ann-Arbor stage at diagnosis n (%)			0.89
2	2 (20 %)	2 (8.3 %)	
3	3 (30 %)	12 (50 %)	
4	5 (50 %)	10 (41.7 %)	
Bulky disease	3 (30 %)	5 (20.8 %)	0.67
Prior lines of treatment [median (min-max)]	6 (4-7)	5 (3-6)	0.62
Previous Radiotherapy n (%)	1 (10 %)	4 (16.7 %)	0.98
Previous autologous transplant	10 (100 %)	21 (87.5 %)	0.54
Withhold nivolumab due to toxicity	1 (10 %)	-	-
Interval between nivolumab bridging therapy and Allogeneic SCT [(days), median (min-max)]	38 (19-85)	-	
Eastern Cooperative Oncology Group Score			0.08
0	4 (40 %)	16 (66.7 %)	
1	5 (50 %)	8 (33.3 %)	
2	1 (10 %)	0	
European Group for Blood &Marrow Transplantation (EBMT)Allograft Risk Score			0.46
2	0	1 (4.2 %)	
3	3 (30 %)	8 (33.3 %)	
4	2 (20 %)	7 (29.2 %)	
5	5 (50 %)	6 (25 %)	
6	0	2 (8.3 %)	

HL, Hodgkin Lymphoma, SCT stem cell transplantation.

at diagnosis were similar in patients from both groups. Stage 3 or 4 disease was present in 80% of patients in the nivolumab group and in 91.7% of patients in the control group ($p = 0.89$). Bulky disease was present at diagnosis in 3 (30%) of patients in the nivolumab group and 5 (20.8%) of patients in the control group ($p = 0.67$). Prior to treatment with allo-SCT, patients in the nivolumab group had received a median of 6 prior lines of therapy for relapsed or refractory disease. Patients in the control group had received a median of 5 prior lines of therapy. Radiation therapy had been administered to 10% of patients in the nivolumab group and to 16.7% of patients in the control group. All patients in the nivolumab group and 21 (87.5%) patients in the control group had a history of auto-SCT. The median number of prior treatments did not differ between groups ($p > 0.05$ for all comparisons). The EBMT allograft score distribution of patients was similar in both groups (Table I).

Patients who received nivolumab as a bridge before allo-SCT received a median of 6 cycles of nivolumab. Patients received a minimum of 4 and a maximum of 9 cycles of nivolumab. Two patients (20%) experienced severe nivolumab toxicity. In one patient, nivolumab treatment was discontinued due to adverse events. Data on allo-SCT are presented in Table II. A complete response (CR) was achieved in 3 patients (30%) in the nivolumab group and in 6 patients (25%) in the control group before allo-SCT. A partial response was achieved in 6 (60%) patients in the nivolumab group and in 10 patients (41.7%) in the control group. One patient (10%) in the nivolumab group had refractory disease prior to allo-SCT. In the control group, 2 patients (8.3%) had stable disease and 8 patients (33.3%) had refractory disease before allo-SCT. Disease status before ASCT was similar in both groups ($p = 0.29$). Stem cell donors in both groups were mostly HLA-identical (90% in the nivolumab

Table II. Data on allo-SCT in study population and control group.

Patients	Group 1 (n: 10)	Group 2 (n: 24)	p
Disease status prior to allo-SCT			0.29
CR	3 (30 %)	6 (25 %)	
PR	6 (60 %)	10 (41.7 %)	
Stable disease	0	3 (12.5 %)	
Refractory Disease	1 (10 %)	5 (20.8 %)	
Stem cell donor			0.63
HLA identical sibling	7 (70 %)	18 (75 %)	
HLA identical unrelated	2 (20 %)	5 (20.8 %)	
Haplo-identical unrelated	1 (10 %)	1 (4.2 %)	
Stem cell source			0.66
Bone marrow	1 (10 %)	2 (8.3 %)	
Peripheral blood	9 (90 %)	22 (91.7 %)	
CD 34 cell dose (10^6/kg)	6.85 ± 0.94	7.06 ± 1.8	0.72
Neutrophil engraftment days [mean (min max)]	15.0 (14-16)	16.8 (10-59)	0.63
Platelet engraftment days [mean (min max)]	11.9 (9-16)	16.5 (9-16)	0.43
Graft versus host disease			0.11
Acute GVHD	3 (30 %)	2 (8.3 %)	
Liver Grade 3	1 (10 %)	1 (4.2 %)	
Skin Grade1	1 (10 %)	1 (4.2 %)	
Skin Grade 3	1 (10 %)	-	
Chronic GVHD	3 (30 %)	7 (29.2 %)	1.0
Lung Grade 2	-	2 (8.3 %)	
Skin Grade1	1 (10 %)	-	
Skin Grade 2	1 (10 %)	1 (4.2 %)	
Liver Grade 1	1 (10 %)	2 (8.3 %)	
Gastrointestinal system Grade 3	-	2 (8.3 %)	
Follow-up after allo-SCT [months median (min-max)]	40 (20-63)	87 (30-123)	< 0.01
100 day mortality	1 (10 %)	4 (16.7 %)	0.54
PFS 30 month	6 (60 %)	11 (45.8 %)	0.69
OS 30 month	8 (80 %)	10 (41.7 %)	0.04

Allo-SCT, Allogeneic stem cell transplantation; CR, Complete response; PR, Partial response; GVHD, Graft versus host disease; PFS, progression free survival; OS, overall survival.

group *vs.* 95.8% in the control group, $p = 0.63$). Neutrophils and platelet engraftment time were similar in both groups. In the post-transplant period, acute GVHD developed in 3 patients (30%) and chronic GVHD developed in 3 patients (30%) in the nivolumab group. In the control group, acute GVHD developed in 2 patients (8.3%) and chronic GVHD in 7 patients (29.2%). The incidence of acute and chronic GVHD was similar in both groups ($p = 0.11$ and $p = 1.0$, respectively). One-hundred-day mortality occurred in 1 patient (10%) in the nivolumab group and in 4 patients (16.7%) in the control group (Table III). This difference was not statistically significant ($p = 0.54$). At the 30-month follow-up PFS was achieved in 60% of patients in the nivolumab group and in 45.8% in the control group ($p = 0.69$). OS was 80% in the nivolumab group and 41.7% in the control group ($p = 0.04$; Table II, Figure 1).

Discussion

In this single-center retrospective study, real-world data from patients with relapsed/refractory HL, who received nivolumab as bridge therapy before allo-SCT, were compared with those from a historical control group that had not received nivolumab before allo-SCT. In the present study, the use of nivolumab as bridging therapy before allo- SCT increased OS. In addition, patients who received nivolumab had a favorable toxicity profile.

An important question discussed in the literature is whether allo-SCT should be performed for consolidation in patients after nivolumab[13]. Many studies[13,17-19] retrospectively compared patients who underwent allo-SCT after nivolumab bridging therapy with those who did not receive allo-SCT. Martinez et al[13] compared data from 27 patients who underwent allo- SCT after nivolum-

Table III. Data and outcome of patients receiving allo-SCT after bridging therapy with nivolumab.

Patient No.	Previous therapy from diagnosis to Nivolumab	Number of Nivolumab cycles	Time from last Nivolumab dose and Allo-SCT (days)	Nivolumab related adverse event	Disease status before Allo-SCT	Post Allo-SCT adverse event	Outcome
1	ABVD, ICE, GDP, Bendamustine + BV, Auto-SCT	9	28	Diarrhea	CR		Death due to CMV pneumonia and septic shock at post – Tx 40th day.
2	ABVD, GDP, Auto-SCT, DHAP, BV	13	32	None	PR		Relapsed at post-Tx 13th month. CR achieved with Nivolumab and Bendamustine
3	ABVD, GDP, Auto-SCT, BV	24	19	Fatigue	PR	Acute grade 3 skin GVHD	CR at post-Tx 53th month
4	ABVD, GDP, Auto-SCT, BV	6	45	Fever	PR		PD, Resistant to salvage bendamustine death at 7th month
5	ABVD, ICE, Vinblastine, RT, GDP, BV Auto-SCT	4	52	None	PR		CR at post-Tx 42th month
6	ABVD, GDP, Auto-SCT, DHAP, BV	8	36	None	CR		CR at post-Tx 50th month
7	ABVD, GDP, Auto-SCT, BV	4	77	Rash	PD	Acute grade 1 skin GVHD	PD detected at post-Tx 3th month. Received 2 cycles of Nivolumab. Developed Chronic Grade 2 liver GVHD. CR achieved with BV, RT and then lenalidomide at post-TX 51th month
8	ABVD, GDP, BV, Auto-SCT	4	85	None	PR	Acute Grade 3 liver GVHD Chronic Grade 1 Skin GVHD	Received eltrombopag CD 34 + Stem cell boost due to loss of engraftment. CR at post-Tx 33 month.
9	ABVD, GDP, BV Auto-SCT	6	39	Transaminase elevation, Fatigue	PR	Chronic grade 2 skin GVHD	CR at Post-TX 37th month. Developed Cyclosporine related TMA at Post-TX 72th day
10	ABVD, ICE, GDP, Bendamustine + BV, Auto-SCT	5	36	None	CR	Chronic Grade 1 Liver GVHD, ITP at Post-TX 283th day	CR at Post-TX 37th month

ABVD, Doxorubicin, bleomycin, vinblastine, and dacarbazine; ICE, Ifosfamide, carboplatin, and etoposide; GDP, Gemcitabine, Dexamethasone, and Cisplatin; BV, Brentuximab vedotin; Auto-SCT; Autologous stem cell transplantation; DHAP, Dexamethasone, cytarabine, and cisplatin; RT, Radiotherapy; CR, Complete response; PR, Partial response; PD, Progressive disease; GVHD, Graft versus host disease; TX, transplant; ITP, Immune thrombocytopenic purpura.

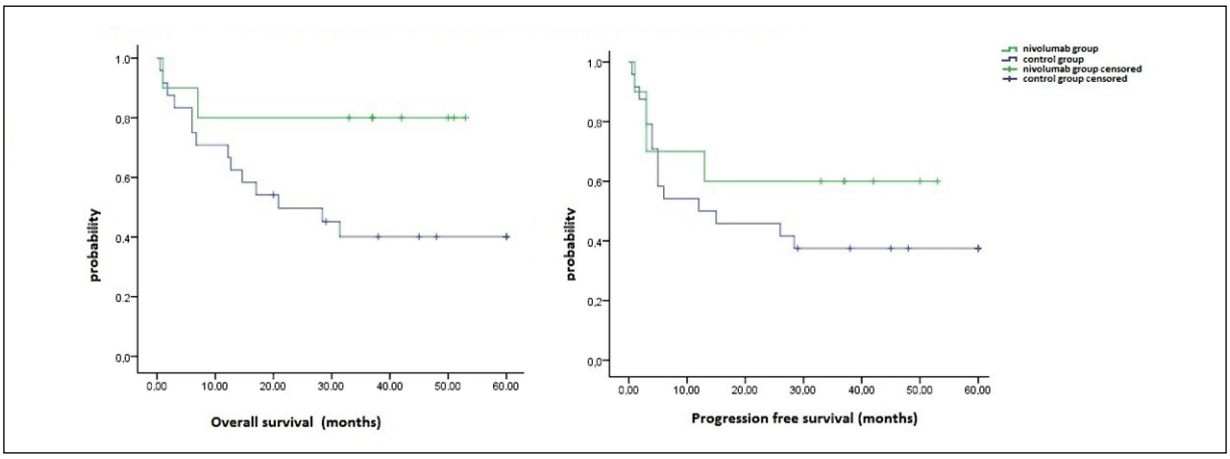

Figure 1. Overall survival and progression free survival in study population and control group.

ab treatment with those from 13 patients who did not undergo allo-SCT. In this study, patients who underwent allo-SCT after bridging with nivolumab had a higher PFS (73.9% *vs.* 27.2%) than those who did not undergo allo-SCT. In addition, all patients not treated with allo- SCT in this study had either relapsed or progressed. However, 4 of the 13 patients in the control group, received allo-SCT previously. In addition, the rate of auto-SCT was higher in patients who had not been treated with allo-SCT after nivolumab. Because of the heterogeneity of the groups in this study, no definitive conclusions could be drawn. However, consolidation with allo-SCT may confer a survival benefit for these patients. Beköz et al[17] published a study of a multicenter experience with nivolumab treatment in 86 patients with relapsed/refractory HL. Fifteen of these patients underwent allo- SCT after treatment with nivolumab. No difference in OS was observed at 24 months between patients who underwent allo-SCT and those who did not (89% *vs.* 92%). However, the two groups were also not homogeneous in terms of disease characteristics. In their study, Manson et al[18] examined 13 patients who were consolidated with allo- SCT after treatment with nivolumab. The control group consisted of 37 patients who were not consolidated with allo-SCT after treatment with nivolumab. They reported that there were fewer relapses in patients treated with allo-SCT, but the OS was similar in both groups.

According to previous data, the overall response to nivolumab was 60-70%[13,20-21]. A complete response (CR) with nivolumab was achieved in approximately 20% of patients[13,20-21]. Data from our study are consistent with these results. In a study of patients who achieved CR with nivolumab, CR persisted 2 years after nivolumab treatment ended[21]. However, because of the limited number of patients in this study, it is not clear how long treatment must be continued in patients who achieve CR with nivolumab. Manson et al[18] reported relapse in 62.2% of patients who did not undergo allo- SCT consolidation after nivolumab treatment. In this study, PFS at 39 months was 84.6% in patients who received allo- SCT consolidation after nivolumab treatment. Among patients who did not receive allo- SCT consolidation after nivolumab treatment, PFS at 39 months was 32.4%. In their series, the subgroup with the best PFS after nivolumab was the group with CR after nivolumab, but PFS decreased significantly in cases where patients had less than a CR. Based on previous data, disease can be expected to progress in a substantial proportion of nivolumab-treated patients with relapsed refractory HL[18]. Therefore, consolidation with allo-SCT must be considered, especially in patients with a worse response than CR. Our current practice is consistent with this view.

In the present study, 30% of patients who received nivolumab developed acute GVHD and 30% developed chronic GVHD after allo- SCT. In the control group, 8.3% of patients developed acute GVHD and 29.2% developed chronic GVHD. The incidence of acute and chronic GVHD was similar in both groups ($p > 0.05$ for all comparisons). In the nivolumab group, acute GVHD of grade 2 or higher was observed in 20% of patients. Chronic GVHD of grade 2 or higher was observed in 10% of patients. These data are consistent with those of Martinez et al[13], who re-

ported grade 2-4 GVHD in 33% of patients who received bridging therapy with nivolumab prior to allo-SCT. In that study, high-dose cyclophosphamide was used for GVHD prophylaxis after transplantation in 51% of patients. The authors believe that this reduced the rate of severe GVHD. In the study by Beköz et al[17], 11 patients were treated with allo-SCT after nivolumab, and 4 (36%) of these patients were found to have GVHD. In their study of 31 patients, Merryman et al[12] found acute GVHD in 45% and chronic GVHD in 33% of patients treated with allo-SCT after a nivolumab bridging. However, 36% of patients in the study had a haploidentical transplant and 10% had a mismatched and unrelated donor. In addition, only 36% of patients had post-transplant cyclophosphamide[12]. The high rate of HLA-identical donor transplantation and the use of cyclophosphamide after transplantation in all patients may have reduced the development of severe GVHD in our study. Another study[22] reported data from 168 patients who had recently undergone allo- SCT after treatment with nivolumab. In that study, PD -1 treatment before allo- SCT resulted in higher PFS and OS than in previous studies. The risk of GVHD increased 2.5-fold in patients who received allo- SCT within 80 days of nivolumab treatment. However, GVHD decreased in patients who received cyclophosphamide after allo-SCT. GVHD also decreased in patients who received more than 10 doses of nivolumab in this study. These results are encouraging because allo-SCT was associated with favorable outcomes. In addition, GVHD rates were reduced by extending the interval between nivolumab and allo- SCT and using cyclophosphamide for GVHD prophylaxis. In our study, nivolumab treatment was discontinued in one patient (10%) due to toxicity. This rate is consistent with the literature, which found that nivolumab was discontinued in 6-16% of patients due to toxicity[13].

This study had some limitations. The number of patients in our study is relatively small, and data from patients who did not undergo allo-SCT after treatment with nivolumab were not included. However, based on the experience at a single center, the group that underwent allo-SCT was homogeneous and therefore clinically relevant.

Conclusions

Our study shows that allo-SCT after bridging therapy with nivolumab provides a survival advantage over allo-SCT without this bridging. Therapy with nivolumab in combination with post-transplant cyclophosphamide does not seem to increase the risk of GVHD.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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