Available online at www.medicinescience.org

ORIGINAL ARTICLE

Medicine Science International Medical Journal

Medicine Science 2020;9(4):1004-7

Nivolumab in relapsed/refractory Hodgkin Lymphoma patients, single center experiences

Ramazan Acar[1], Murat Yildirim[2]

[1]*Science Health University, Gulhane School of Medicine, Department of Medical Oncology, Ankara, Turkey*
[2]*Science Health University, Gulhane School of Medicine, Department of Medical Hematology, Ankara, Turkey*

Received 01 July 2020; Accepted 06 September 2020
Available online 20.11.2020 with doi: 10.5455/medscience.2020.07.125

Abstract

Hodgkin Lymphoma (HL) is one of the hematological malignancies where the inflammatory process is quite high, immunotherapy agents are frequently used and successful results are obtained. We aimed to show real-life data on health outcomes in adult patients withrecurrent or refractory HL who received nivolumab (immune checkpoint inhibitory). We analyzed the data of 15 patients who received nivolumab after or before high dose chemotherapy (HDCT) for relapsed or refractory HL from 2010 to 2020. Overall response rate (ORR), overall survival (OS) and progression-free survival (PFS) of the patients were evaluated. 15 patients were observed in this study. The mean age of the study group was 26.9 ±10.9 years. 40% of the patients were female (n=6). Overall response rate (ORR) was 80 %. The median overall survival (OS) and progression-free survival (PFS) were 50.7 months (95% CI: 37.2-64.2) and 46.2 months (95% CI: 32.9-59.5), respectively. 1-year OS and PFS rates were 90.9% and %88.2, respectively. 5-year OS rate was 67.3%. Nivolumab treatment is a safe, effective and excellent treatment option for relapsed or refractory adult HL patients with a good ORR, OS and PFS time.

Keywords: Nivolumab, Hodgkin Lymphoma, immunotherapy

Introduction

Hodgkin Lymphoma (HL) is one of the hematological malignancies where the inflammatory process is quite high, immunotherapy agents are frequently used and successful results are obtained [1]. The prognosis of relapsed or refractory HL patients after high dose chemotherapy (HDCT) or after multi-lines treatments is poor [2]. Chromosome 9p24.1 amplification causes Programmed Death Ligand -1 (PDL-1) and Programmed Death Ligand-2 (PDL-2) overexpression in HL [3]. This overexpression in Reed Steenberg cells leads to an increase in PDL-1 and PDL-2, which are involved in immune checkpoints. PDL-1 and PDL-2 are both binding the PD-1 receptors which leads a reversibleinhibition of T cell activation and proliferation [4]. Thus, it causes to successful treatment with immune checkpoint inhibitors that increases T cell immunity [4]. For this purpose, immunotherapy agents such as nivolumab, pembrolizumab and atezolizumab are used in treatment [5]. The Checkmate 205 study demonstrated the effectiveness of Nivolumab immunotherapy in Relapsed / refractory HL patients [5].

***Coresponding Author:** Ramazan Acar, Science Health University, Gulhane School of Medicine, Department of Medical Oncology, Ankara, Turkey.
E-mail: dr_racar@yahoo.com

We also use this treatment option for such patients after or before HDCT in Turkey. Our Hematology and Medical Oncology Departments have experience in all kind of Lymphoma treatments. And we have good results.

We aimed to demonstrate the real-life data about nivolumab immunotherapy in relapsed or refractory HL patients andshow the overall response rate (ORR), progression free survival (PFS), overall survival (OS) and toxicities of this treatment choice.

Material and Methods

Study design and Cases

The study was carried out by investigating the patients with relapsed and refractory adult HL had received nivolumab in University of Health Science, Gulhane Research and Training Hospital, Department of Medical Oncology and Hematology between October 2010 and May 2020 in diagnosis, treatment, complications outcomes. The study is a single-center, retrospective study.

A retrospective case control study was carried out with 15 cases comprising previously diagnosed and treated or currently on

a nivolumab treatment forHL in terms of demographics, cancer specific features, including histology, stage of the cancer, previous or ongoing treatmentand previousradiotherapy.

The patients received nivolumab at a dose 3mg/kg every two weeks until progression or undesirable toxicities [5]. All patients were called to the hospital every 3 months to check for response control after beginning of nivolumab. We used [18F] fluorodeoxyglucose (FDG) positron emission tomography- computed tomography (PET-CT), ultrasound or computed tomography for tumor assessment.

The primary endpoint of this study is to assess the PFS and OS periods. Secondary endpoints were to identify clinical factors prognostic for disease progression after nivolumab treatment, and to define the safety and the toxicity profile of nivolumab.

Statistical Analysis

Medical records who admitted to the Department of Medical Oncology and Hematology at the University of Health Science, Gulhane Research and Training Hospital and eventually diagnosed with HL were investigated whether they previously or currently had received nivolumab. Medical records of suitable cases were enrolled in a SPSS data-sheet by the registered staff of Department of Oncology at Health Science University.

Patients demographics, clinical and biochemical features, clinical and radiologic outcomes were recorded in an SPSS v 22.0 (SPSS Inc., Chicago, IL USA) data sheet considering the patients confidentiality. Data was accessible only by the authorized institutional staff and caregivers. Students' t-test was utilized for the test due to the normal distribution of data. Demographic indices provided in mean values with the standard deviation or median values as appropriate. Frequencies noted in numbers with percentiles. Survival analysis was conducted utilizing Kaplan-Meier tables and survival plots provided.

Results

We determined that 105 patients were followed up with diagnosis of HL between October 2010 and May 2020. 15 (14,3%) of the patientsreceived nivolumab. The mean and median age of the study group was 26.9 ±10.9 years and 24 years (IQR;21-30), respectively. 40% of the patients were female (n=6). Three patients were stage 3B and the others were stage 4 at the time of diagnosis. Tumor histology revealed nodular sclerosing type HL in 10 patients (66.7%), three patients (20 %) showing lymphocyte reach type HL and two patients (13.3%) showing mixt cellular type HL at diagnosis. Spleen was the most seen metastatic site 4 (26.7 %) among the patients included in the study. Liver and Lungs were the other most common metastatic sites, respectively. Two (13.3%) of them had more than two metastatic sites.Fourteen patients receivedHDCT. One patient did not need HDCT. This patient had received nivolumab as third line therapy.Four (26.6%) of the patients treated with nivolumab as fifth line therapy. Ten patients (66.7%) treated with nivolumab as sixth line therapy (Table 1). Seven patients had complete response (46.6 %), five patients had partial response (33.3 %) and two patients had stabile disease (13.3%) . Progression was observed in one patient. This patient died due to the disease progression. Overall response rate (ORR) was 80%. Later in long term follow up period two patients died due to the drug related pneumonitis.All cases received comprising Adriamycin, Bleomycin, Vincristin and Dakarbazin (ABVD) chemotherapy regimenas first line therapy. They underwent different combination therapies for the second, third and fourth lines (Table 1).

Table 1. The demographic and disease-related characteristics of the patients

Features	**n (%)**	**Mean ± SD Median**
Age (years)	15 (100)	26.9±10.9 24 (21-30)
Gender		
Male	9 (60)	
Female	6 (40)	
Histopathology		
Nodular Sclerosing type	10 (66.7)	
Mixed cellular type	2 (13.3)	
Lymphocyte -rich type	3 (20)	
Stage at the Time of Diagnosis		
3B	3 (20)	
4A	5 (33.3)	
4B	7 (46.7)	
Site of metastases		
No metastases	3 (20)	
Liver	3 (20)	
Spleen	4 (26.7)	
Lung	3 (20)	
More than 1 sites	2 (13.3)	
The response of the patients after Nivolumab		
Stable response	2 (13.3)	
Partial response	5 (33.3)	
Complete response	7 (46.7)	
Progressive disease	1 (6.7)	

The treatments lines patients received before Nivolumab						
-Treatments	**First line: n(%)**	**Second line: n(%)**	**Third line: n(%)**	**Fourth line: n(%)**	**Fifth line: n(%)**	**Sixth line:n (%)**
-ABVD	10 (66.7)	-	-			
-ABVD +IFRT	5 (33.3)	-	-			
-ICE	-	3 (20)	4 (26.6)			
-DHAP	-	10 (66.7)				
-BEACOPP	-	2 (13.3)				
-Brentuximab Vedotin	-	-	1 (6.7)			
-NİVOLUMAB			1 (6.7)		4 (26.6)	10 (6.7)
-HDCT	-	-	9 (60)	5 (33.3)		
GemOX					1 (6.7)	
Bendamustin						1 (6.7)

Abbreviations:HDCT: High dose ChemoTherapy, ABVD: Adriamycin, Bleomycin, Vincristin and DakarbazinI FRT: Involved Field Radiotherapy, DHAP: High Dose Ara-C and Dexamethasone , ICE: Ifosfamide, Carboplatin and Etoposide, BEACOPP: Bleomycin, Etoposide, Adriamycin, Cyclophosphamide,Vincristine, Procarbazine and Prednisone GemOX: Gemcitabine and oxaliplatin

The mean and median follow up time following nivolumab was 61.4±34.1 months and 49 months (IQR;41-70), respectively. The median overall survival (OS) and progression free survival (PFS) were as follows; 50.7 months (95% CI: 37.2-64.2) and 46.2 months (95% CI: 32.9-59.5), respectively (Figure 1 and 2). OS and PFS at 12 months were 90.9% and %88.2, respectively. The Median OS was 93 months (95% CI: 32.6-153.4) and 5 years OS was 67.3% among all lines with chemotherapy, HDCT and nivolumab.

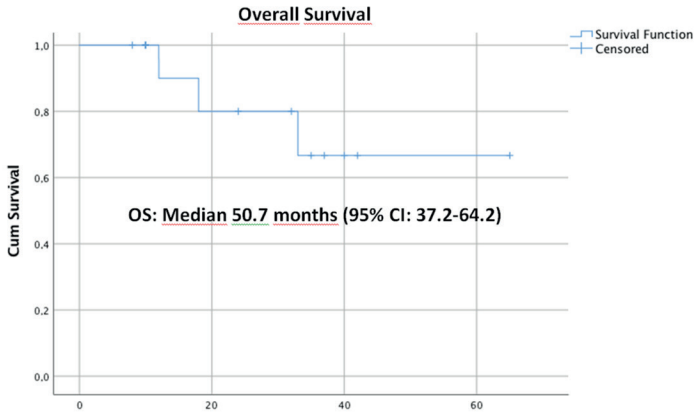

Figure 1. Overall survival of patients receivedNivolumab (Kaplan-Meier Curve)

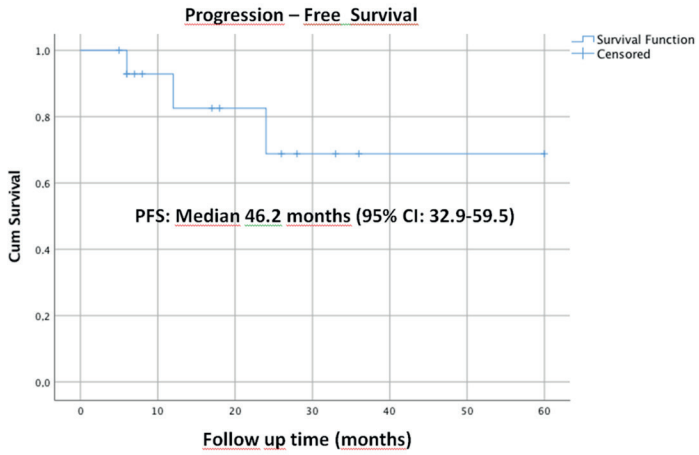

Figure 2. Progression Free Survival of Patients receivedNivolumab (Kaplan-Meier Curve)

The numbers of side effects related to nivolumab are demonstrated in Table 2. Leukopenia, anemia, thrombocytopenia, neurotoxicity, febrile neutropenia, diarrhea, vomiting/nausea, pneumonitis, arthritis, hypothyroidismwereobserved. Two patients had grade 4 thrombocytopenia, neuropathy and pneumonitis. No bleeding was observed.Both of them died due to the pneumonitis. The other patients had nolife-threateningtoxicity. Some of them had received steroid for arthritis and pneumonitis until the side effect disappeared. They are still alive.

Table 2. Toxicities of Nivolumab

	All n (%)	Grade 3 and 4 n (%)
Leukopenia	5 (33.3)	1 (6.7)
Anemia	6 (40)	1 (6.7)
Thrombocytopenia	6 (40)	2 (13.3)
Febril Neutropenia	3 (20)	1 (6.7)
Neurotoxicity	5 (33.3)	2 (13.3)
Vomiting/Nausea	7 (46.6)	0
Diarrhea	10 (66.7)	0
Pneumonitis	2 (13.3)	2 (13.3)
Artritis	3 (20)	0
Hypothyroidism	5 (33.3)	0

Discussion

In most patients with HL, a complete remission response is obtained after initial treatment. However, relapse may develop in the follow-up period in approximately 10-15% of early stage HL patients and approximately 15-30% of late stages [6]. The main treatment goal in relapse refractory HL is long-term disease control, with few side effects and complications. Although salvage chemotherapy provides a complete remission response in these patients, HDCT is needed [7]. Treatment regimens ofIfosfamide, carboplatin, etoposide (ICE), High Dose Ara-C, Dexamethasone(DHAP), gemcitabine, vinorelbine, pegylated liposomal doxorubicin(GVD), gemcitabine, dexamethasone, cisplatin (GDP), brentuximab vedotin (BV), nivolumab and pembrolizumab are used as salvage chemotherapy. Compliance with HDCT, functional response to Salvage chemotherapy, bulky disease, duration of remission, previous treatments and comorbid diseases are important in salvage treatment selection [7]. There is no comparative randomized study of salvage chemotherapy regimens. Real-life data analysis of nivolumab treatment, one of the immunotherapy agents used as salvage treatment option in relapse refractory HL, has been performed in our study. Immunotherapy agents have been used rapidly in almost all types of cancer recently. Nivolumab is preferred as a treatment option after HDCT or post-transplant BV use in relapse refractory HL worldwide [5]. Also pembrolizumab treatment is preferred as a treatment option after using three or more treatment steps, after HDCT and BV use or in patients who are not suitable for HDCT [8].

Immunotherapies, especiallyCytotoxic T-lymphocyte-associated protein 4(CTLA-4), PD-1 and PDL-1 inhibitors (Immune checkpoint inhibitors; ICI), have made us all happy to see statistically significant prolonged survivals and ongoing successful response times in most types of cancer [9,10]. In addition, seeing and treating the side effects that occur during these treatments has also improved our medical oncologists' experience in the immune system.

Some studies showed ORRs in the range of 65-73%. Armand et al observed ORR in 65%, 68%,73% and 72% of patients for different cohorts in Checkmate 205 trial [5]. Chen et al. observed ORR in 69 % of patients after pembrolizumab in keynote 087 trial. Both of these studies had good results. Diefenbach et al used BV + Nivolumab for eight relapsed or refractory HL patients. The patients received nivolumab for 16 cycles to two years. They showed 100% ORR [11]. We observed ORR in 80% of 15 patients. Later progression developed in one patient. Three of them died in follow up (20%, n=3). Only one patient died due to the progression. Twelve patients are still alive. All patients are still receiving treatment.

Armand et al. showed an average of 14.7 months of PFS after Nivolumab [5]. Median OS was not reach in any cohorts. They had different cohort groups due to the nivolumab receiving lines. All cohorts had different PFS. Diefenbach et al. showed 100% PFS with a median follow up of 0.3 years [11]. In our study we observed 50.7 months OS and 46.2 months PFS. OS and PFS were 90.9% and 88.2% at 12 months, respectively. The OS rate for five years was 67.3%. Our results were better than literature before.

Armand et al. reported that most common drug related toxicities were fatigue, diarrhea and infusion related reactions (23%, 15% and 14%, respectively). The most common grade 3-4 toxicities were lipase increases, neutropenia and ALT (alanin aminotransferase) increases (5%, 3% and 3%, respectively). 29 patients died in their cohorts. No deaths were related to the nivolumab [5]. Chen et al reported that most common treatment related toxicities were hypothyroidism and pyrexia (12.4% and 10.5%). The most common grade 3-4 toxicities were neutropenia, dyspnea and diarrhea. Nine patients (4.3%) discontinued the treatment because of toxicities (myocarditis, myelitis, myositis, pneumonitis, infusion related reactions and cytokine release syndrome). Two patients died due to the drug related toxicities [8]. Diefenbach et al reported that only two patients had grade 3 pneumonitis and dyspnea. BV plus nivolumab combination was extremely well tolerated [11]. In our study cohort we observed that most common toxicities were diarrhea, vomiting/nausea, anemia and thrombocytopenia. Most common grade 3-4 toxicities were pneumonitis, thrombocytopenia and neurotoxicity. Two patients died due to the pneumonitis (drug related). Other toxicities were well tolerated and treated with steroids. The patient who died were followed up along time period. And they had four or more treatment lines before nivolumab. Overall the toxicities of Nivolumab were acceptable.

Although this study had a small sample size of relapsed or refractory HLpatients with further treatments lines and long follow-up. We observed excellent OS and PFS. There are some limitations to report. It is a retrospective study, and the patient population was relatively heterogeneous. The patient sample size was small. HL patients in this study underwent HDCT at an experienced high-volume referral center for relapsed or refractory HL. We believe that these patients need multidisciplinary expertise and hence should be treated at centers of stem cell transplantation excellence. The strengths of the study include nivolumab in further lines. The results cannot be applied to other countries with different cancer epidemiology and practice.

In conclusion, overall nivolumabshowed excellent results in both relapsed and refractory HL patients. It remains one of the best determined systemic treatment options. Also, the treatment was associated with good efficacy and tolerability.

Conflict of interests

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

Financial Disclosure

All authors declare no financial support.

Acknowledgements

We thank to Management of the Gulhane Training and Research Hospital and our patients and their families who participated in the research devotedly. The contributions of the authors were; General supervision of research: RA; writing assistance: RA,MY data collection: RA,MY ; responsibility for presentation and logical explanation of results: RA, MY; final approval of the manuscript: RA, MY.

Ethical approval

The Ethics Committee of University of Health Science, Gulhane Researh and Training Hospital approved the studywith 2020-256 ethical committe number at 09 June, 2020.

References

1. Kansara R, Speziali C. Immunotherapy in hematologic malignancies. Curr Oncol. 2020;27:124.
2. Von Tresckow B, Müller H, Eichenauer et al. Outcome and risk factors of patients with Hodgkin Lymphoma who relapse or progress after autologous stem cell transplant. Leukem lymphom. 2014;55:1922-4.
3. Green MR, Monti S, Rodig SJ, et al. Integrative analysis reveals selective 9p24. 1 amplification, increased PD-1 ligand expression, and further induction via JAK2 in nodular sclerosing Hodgkin lymphoma and primary mediastinal large B-cell lymphoma. Blood, J American Societ Hematol. 2010;116:3268-77.
4. Ansell SM, Lesokhin AM, Borrello I et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. New England J Med. 2015;372:311-9.
5. Armand P, Engert A, Younes A et al. Nivolumab for relapsed/refractory classic Hodgkin lymphoma after failure of autologous hematopoietic cell transplantation: extended follow-up of the multicohort single-arm phase II CheckMate 205 trial. J Clinic Oncol. 2018;36:1428.
6. Eich HT, Diehl V, Görgen H et al. Intensified chemotherapy and dose-reduced involved-field radiotherapy in patients with early unfavorable Hodgkin's lymphoma: final analysis of the German Hodgkin Study Group HD11 trial. J Clinic Oncol. 2010;28:4199-206.
7. Martin N, Borchiellini D, Coso D et al. High-dose chemotherapy with carmustine, etoposide, cytarabine and melphalan followed by autologous stem cell transplant is an effective treatment for elderly patients with poor-prognosis lymphoma. Leukem lymphom. 2015;56:2379-87.
8. Chen R, Zinzani PL, Lee HJ et al. Pembrolizumab in relapsed or refractory Hodgkin lymphoma: 2-year follow-up of KEYNOTE-087. Blood. 2019;134:1144-53.
9. Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. Overall survival with combined nivolumab and ipilimumab in advanced melanoma. New England J Med. 2017;377:1345-56.
10. Reck M, Rodríguez-Abreu D, Robinson AG et al. Pembrolizumab versus chemotherapy for PD-L1–positive non–small-cell lung cancer. New England J Med. 2016;375:1823-33.
11. Diefenbach CS, Hong F, David KA et al. A phase I study with an expansion cohort of the combination of ipilimumab and nivolumab and brentuximab vedotin in patients with relapsed/refractory Hodgkin lymphoma: a trial of the ECOG-ACRIN Cancer Research Group (E4412 Arms D and E). American Soci Hematol. 2020;7:660-70.