The Effect of Nivolumab in Pediatric Malignant Tumors: A Single Center Experience with Nine Children

Veysel GOK[1], Firdevs AYDIN[1], Alper OZCAN[1], Zehra Filiz KARAMAN[2], Ebru YILMAZ[1], Orhan GORUKMEZ[3], Ozlem GORUKMEZ[3], Atil BISGIN[4,5], Musa KARAKUKCU[1], Turkan PATIROGLU[1], Ekrem UNAL[1,6,7]

[1] Erciyes University, Faculty of Medicine, Department of Pediatrics, Division of Pediatric Hematology and Oncology
[2] Erciyes University, Faculty of Medicine, Department of Radiology, Division of Pediatric Radiology
[3] Bursa Yüksek Ihtisas Training and Research Hospital, Department of Medical Genetics
[4] Çukurova University, Faculty of Medicine, Department of Medical Genetics
[5] Çukurova University, Adana Genetic Diseases Diagnosis and Treatment Center (AGENTEM)
[6] Medical Point Hospital, Pediatric Hematology and Oncology Clinic
[7] Hasan Kalyoncu University, Faculty of Medicine, School of Health Science.

ABSTRACT

Nivolumab is an inhibitor of programmed cell death 1 (PD-1), which enables activated T cells to attack the tumor cells. Although the utilization of nivolumab in adulthood cancers is more common, experience in childhood has been increasing recently. Herein, pediatric cases received nivolumab for distinct cancers are presented. The data of nine patients under the age of 18 years who received nivolumab for various cancers in the Pediatric Oncology clinic between January 2019-December 2022 were obtained. Nivolumab was administered intravenously at a dose of 3 mg/kg with 30 minutes infusion every two weeks. Patients' clinical, cancer types, response to primary treatment, comorbidities, and outcomes of nivolumab were evaluated. Nivolumab was utilized for non-Hodgkin lymphoma, classical Hodgkin lymphoma (cHL), central nervous system, germ cell and gastrointestinal system cancers. Four out of nine patients had constitutional mismatch repair deficiency (CMMRD) syndrome and 2/4 patients developed secondary cancers during the nivolumab. The median dose and duration of nivolumab were 10 doses (4-32 doses) and 6 months (2 to 17 months), respectively. The median follow-up period was 25 months (2-46 months). Nivolumab achieved progression free survival in immature teratoma, cHL and T-Lymphoblastic lymphoma (T-LBL) with 46 months, 22 months, and 31 months, respectively. Only one patient had severe generalize edema attributed to nivolumab. We observed that although encouraging outcomes with nivolumab in cHL, immature teratoma and T-LBL, it failed to prevent glioblastoma progression in children with CMMRD. In summary, nivolumab may be effective in selected childhood cancers.

Keywords: Cancer, Childhood, Lymphoma, Nivolumab, PD-1

INTRODUCTION

Many malignant diseases are seen in childhood, such as leukemia, brain tumors and lymphoma, as well as neuroblastoma, Wilms tumor, rhabdomyosarcoma, and bone tumors.[1-3] Although survival has improved dramatically with current chemotherapies and good care, refractoriness and disease relapse are unfortunately not uncommon in a group of patients. Despite high rate of remission, a group of patients may become disabled or die due to cancer progression or infections and side effects triggered by chemotherapies.[4] For this reason, target therapies and immunomodulator medications have been utilized in recent years to minimize side effects and provide more effective treatment.[5] For example, immune therapies such as chimeric antigen receptor-modified T cells (CAR-T cells) and blinatumomab (Bi-specific T-cell engager) in relapsed or refractory pediatric B-cell acute lymphoblastic leukemia (ALL), and dinutuximab (anti-GD2) in high-risk neuroblastoma have shown promising results.[6-10]

The immune system, consisting of innate and adaptive immunity, is naturally designed to eliminate the development of cancer. Overexpression of immune checkpoint (IC) receptors and their ligands inhibits this control, thereby leading to cancer progression and metastasis. The discovery and use of monoclonal antibodies targeting these ICs and their ligands is promising for cancer treatment.[11,12] Ipilimumab, the first IC inhibitor against cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), showed good outcomes in clinical trials and was approved for the treatment of metastatic malignant melanoma (MM) in adults in 2011.[13] Since then, clinical trials for the programmed cell death 1 (PD-1) receptor and its ligand, T-cell lymphocyte activation gene 3 (LAG-3) and other ICs have continued more widely.

PD-1 receptor was first discovered by Ishida in 1992. PD-1 is an IC receptor expressed by activated T cells and binds to its ligands (PD-L1 and PD-L2) expressed on tumor cells, causing selective immunosuppression, and preventing the immune system from inactivating the tumor.[14] Currently, CTLA-4 and PD-1 inhibitors are well tolerated and safely used in adulthood cancers. Experience with IC inhibitors such as PD-1 blockade in pediatric cancers is limited. Nivolumab and pembrolizumab are the monoclonal antibodies that block the binding of PD-1 to its ligands, activating T cells against the tumor cells.[15]

Nivolumab is a fully human IgG4 monoclonal antibody that targets the PD-1 receptor located on activated T cells, B cells and myeloid cells. Although nivolumab is more commonly utilized in adulthood cancers, it has been shown to be effective in hematologic malignancies in all age groups.[16-18] The efficacy of nivolumab in solid cancers such as central nervous system (CNS) and gastrointestinal system (GIS) tumors has also been reported in case series.[15-19] In this paper, we present our experience with nivolumab in nine pediatric patients with various refractory cancers.

PATIENTS AND METHODS

Nine patients under the age of 18 years who received nivolumab for different cancers at Erciyes University Pediatric Hematology and Oncology clinic between January 2019 and December 2022 were included in the study. Nivolumab was administered intravenously as a 30-minute infusion at a dose of 3 mg/kg every two weeks. Nivolumab was initiated after a primary chemotherapy regimen in all patients. Nivolumab was withdrawn due to disease progression, development of secondary cancer, severe side effects or death. Data of patients receiving nivolumab were obtained from patient records and folders. Demographic characteristics of patients, cancer types, response to primary chemotherapy, other comorbidities, duration of nivolumab treatment, efficacy and side effects were evaluated. The data were detailed in the results section and supplemental file. Statistical analysis could not be performed due to the limited number of cases.

This study was approved by Erciyes University Ethics Committee (2022/131). Written informed consent was also obtained from the participants.

RESULTS

Characteristics of Patients and General Results

The details of nine patients (5 girls, 4 boys) who received nivolumab are presented in Table 1 and detailed in the following sections. Nivolumab was started to patients at a median age of 11 (4-17) years. The median dose and duration of nivolumab were 10 doses (4-32 doses) and 6 months (2 to 17 months), respectively. The median follow-up duration after the first dose of nivolumab was 25 (2-46) months. Nivolumab was given to patients with relapsed, refractory, or concomitant a cancer with constitutional mismatch repair deficiency (CMMRD) syndrome, as well as patients with H3K27M mutant brain malign tumors.

Malignant diseases for which nivolumab was used; non-Hodgkin lymphoma (NHL), classical Hodgkin lymphoma (cHL), central nervous system (CNS) malignant tumors, germ cell malignant tumor, gastrointestinal malignant tumor. One patient (patient 9) with refractory cHL was treated with nivolumab after autologous hematopoietic stem cell transplantation (HSCT). In four patients (patients 1, 5, 7, 8), homozygous pathogenic variants in mismatch repair (MMR) genes were detected as a result of ge-

Table 1. The clinical information of patients

Patient no	Age at diagnosis (years), gender	Diagnoses	Initial therapy	Tumor status prior to nivolumab	Nivolumab treatment (dose/duration)	Adverse events of nivolumab	Reason for nivolumab termination	Genetic analysis	Response to nivolumab/ Final status
1	16, girl	-Grade 4 GBM -CRC	-Surgery -RT+TEM -FOLFOX	-Residual tumor in CNS -CRC	4 d/2m	-Fatigue -Vomiting	Progression and death	Homozygous c.1444C>T variant in MSH6	No/Not alive
2	6, boy	-DMG (Grade 4)[a]	-Surgery -RT	-Residual tumor in CNS	11 d/6m	No	Progression	NS	No/Not alive
3	9, girl	-Immature teratoma (Grade 3)	-Surgery -JEB -IP	-Residual tumor in abdomen	32 d/16m	-Severe edema -Loss of appetite	Nivolumab side effect	NS	Yes/Stable disease
4	4, girl	-Sacral yolk sac tumor	-Surgery -JEB -ICE -Autologous HSCT	-No residual tumor after surgery	4 d/2m	-Loss of appetite	Progression	NS	No/Not alive
5	13, boy	-T-LBL -GB	-NHL-BFM 2012	-Tubular adenoma -Glial tumors in CNS	30 d/17m	No	GBM developed	Homozygous c.478C>T variant in MSH6	No/Not alive
6	12, girl	-DIPG (Grade 4)[a]	-Surgery -RT -TEM	-Residual tumor in CNS	6 d/3m	-Fatigue -Vomiting	Progression	NS	No/Not alive
7	13, girl	- T cell and histiocyte rich B-LBL -GB	-R-CHOP -Glial tumors in CNS	-Refractory disease	13 d/7m	-Edema -Vomiting	GBM developed	Homozygous frameshift mutation in MSH6	No/Not alive
8	8, boy	-T-LBL	-NHL-BFM 2012	-Glial tumors in CNS	12 d/6m	No	Drug reimbursement problem	Homozygous c.478C>T variant in MSH6	Yes/In remission
9	17, boy	-HL	-ABVD -BICE -Autologous HSCT	- Residual disease after transplant	6 d/3m	No	Stable disease	Normal WES	Yes/Stable disease

***Abbreviations**: d, dose; m, months; NS, not studied; GBM, glioblastoma multiforme; CRC, colorectal carcinoma; DMG, diffuse midline glioma; DIPG, diffuse intrinsic pontine glioma; T-LBL, T-cell lymphoblastic lymphoma; B-LBL, B-cell lymphoblastic lymphoma; HL, Hodgkin lymphoma; RT, radiotherapy; TEM, temozolomide; FOLFOX, oxaliplatin+5 fluorouracil; IP, ifosfamide+paclitaxel; JEB, carboplatin+etoposide+bleomycin; NHL-BFM, non-Hodgkin lymphoma-Berlin-Frankfurt-Münster; R-CHOP, rituximab+cyclophosphamide+doxorubicin+vincristine+prednisolone; ABVD, adriamycin+bleomycin+vincristine+dacarbazine; BICE, brentuximab+ifosfamide+carboplatin+etoposide; HSCT, hematopoietic stem cell transplantation; CNS, central nervous system; WES, whole exome sequencing.*

[a] *H3K27M mutant glioma*

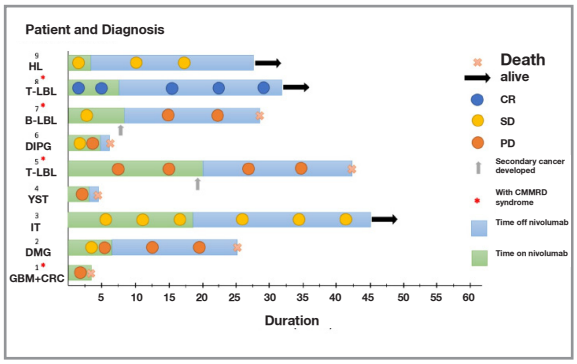

Figure 1. Nivolumab therapy responses and disease outcome of all patients. HL, Hodgkin lymphoma; T-LBL, T lymphoblastic lymphoma; B-LBL, B lymphoblastic lymphoma; DIPG, diffuse intrinsic pontine glioma; YST, yolk sac tumor; IT, immature teratoma; DMG, diffuse midline glioma; GB, glioblastoma; CRC, colorectal carcinoma; CR, complete response; SD, stable disease; PD, progressive disease; CMMRD, constitutional mismatch repair deficiency.

netic study. These mutations have been associated with CMMRD syndrome. Children with CMMRD syndrome had NHL, glioblastoma and colorectal cancer. Three out of four patients developed secondary cancer. Patients 5 and 7 developed glioblastoma during the nivolumab treatment.

The Outcomes of Nivolumab Treatment

The outcomes of the nivolumab in all patients were summarized in Figure 1. Six out of nine (66.7%) patients had an insufficient response to nivolumab. Nivolumab was discontinued due to disease progression, development of secondary cancers or death. Three patients diagnosed with cHL, immature teratoma or T-LBL had favorable response to nivolumab. Unfortunately, it was discontinued in patient 3 due to development of severe generalized edema contributed to the nivolumab. The cancer of patient 8 was in remission with nivolumab, but the treatment was terminated due to reimbursement problems. Patient 9 received 6 doses of nivolumab after autologous HSCT and now has a stable disease. Six patients died due to disease progression and three patients are in remission or have stable disease. There was severe generalized edema throughout the body in a patient directly attributed to nivolumab as treatment-related adverse events (TRAEs). Other side effects included loss of appetite, vomiting, weakness, and edema.

Treatment Details of the Patients

Patient 1, a 16-year-old girl, was diagnosed with WHO grade 4 glioblastoma. She underwent subtotal excision, then radiotherapy (RT) + temozolomide, and subsequently only temozolomide treatment. A mass was detected in the descending colon five months after the end of treatment. The mass was subtotal resected, and pathology was reported as adenocarcinoma. The patient was genetically diagnosed with CMMRD syndrome.[20] After two cycles of oxaliplatin+5-fluorouracil (FOLFOX) chemotherapy, nivolumab was initiated as monotherapy due to disease progression. After four doses of nivolumab, the masses in the colon and

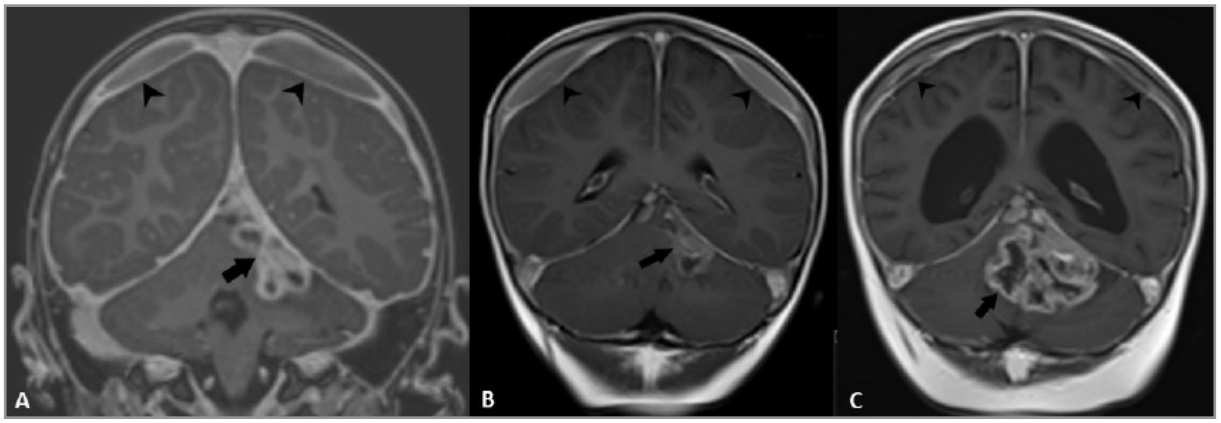

Figure 2. Coronal T1 weighted contrast-enhanced brain MRI of patient 2. A tumor with contrast enhancement is seen in left cerebellar hemisphere adjacent to the tentorium (arrow) and subdural collections are seen surrounding both cerebral hemispheres (arrowheads) before the nivolumab treatment **(A)**. There was no obvious difference after 5th dose of nivolumab **(B)**. The tumor (arrow) is enlarged, and Subdural collections are regressed after 11th dose of nivolumab **(C)**.

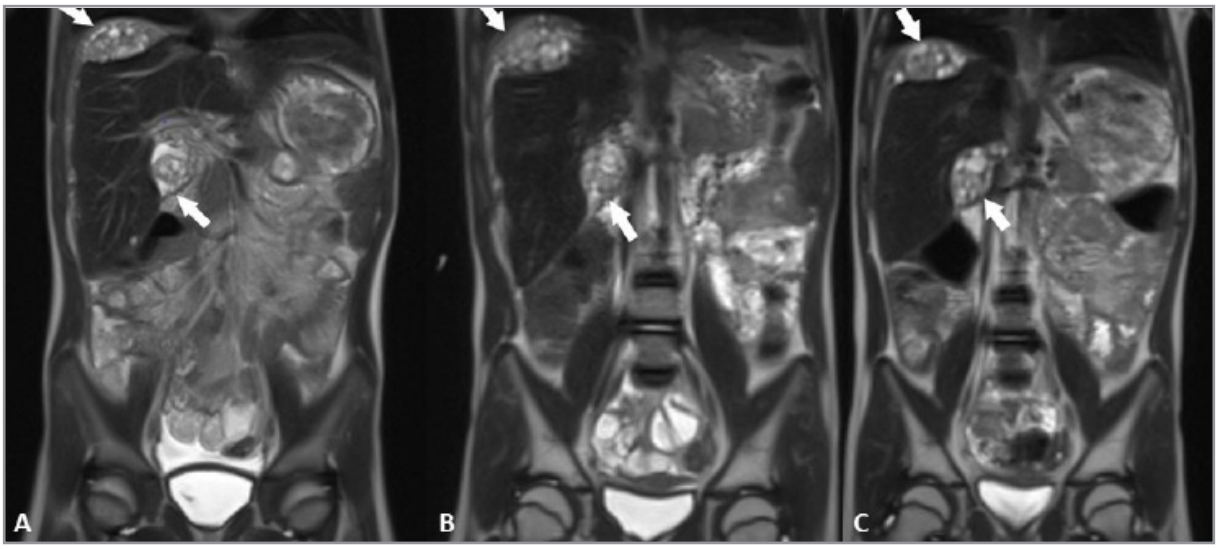

Figure 3. Coronal T2 weighted thorax MRI of patient 3. Subdiaphragmatic and liver hilus located tumors are seen (arrows) and they are stable during the nivolumab treatment.

CNS progressed, so nivolumab was discontinued. Fatigue and vomiting were observed as adverse events of nivolumab. He died due to respiratory failure one month later.

Patient 2, 6 years old male, diagnosed with H3K27M mutant WHO grade 4 diffuse midline glioma (DMG) in the cerebellar vermis. Radiotherapy was applied for six weeks after surgery, followed by nivolumab. After five doses of nivolumab, the mass was stable on magnetic resonance imaging (MRI) (Figures 2A and 2B). In the 6th month (11 doses) of nivolumab, the existing mass enlarged (Figure 2C). So, the drug was discontinued. He died about 25 months after the beginning of nivolumab. There wasn't an adverse event attributed to nivolumab.

Patient 3, a 9-year-old girl, was admitted with abdominal distension and diagnosed as an immature teratoma in the left adnexal site. After surgery, a course of carboplatin, etoposide, and bleomycin (JEB) chemotherapy was initiated. After four courses of JEB chemotherapy, Ifosfamide and paclitaxel (IP) cycle was given due to progression. After two cycles of IP, nivolumab was started as monotherapy due to diffuse involvement in the abdomen on MRI (Figure 3A). A total of 32 doses of nivolumab were given for 16 months. The disease was stable in intermittent MRI scans (Figures 3B and 3C). Nivolumab was discontinued due to the development of severe generalized edema as a drug side effect. The follow-up period was 46 months, and the disease is stable currently.

Patient 4, a 4-year-old girl, was diagnosed with yolk sac tumor in the sacral region at the age of 2 years. The disease was refractory after six cycles of JEB chemotherapy. Therefore, three cycles of ifosfamide, carboplatin and etoposide (ICE) chemotherapy were given and then the patient underwent autologous HSCT. Seven months after transplantation, a new mass developed on the anterior abdominal wall. The tumor was total resected and nivolumab was initiated as monotherapy. After four doses of nivolumab, treatment was discontinued due to relapse of the tumor at the same region. There was only anorexia as a side-effect attributed to nivolumab. She died almost 3 months after the beginning of nivolumab.

Patient 5, a 13-year-old boy, was diagnosed with T cell NHL at the age of 4 years and cured after the NHL-Berlin-Frankfurt-Münster (BFM) 2012 protocol. Unfortunately, he relapsed at the age of eight. Remission was achieved after relapse treatment of NHL. At the age of 13 years, colonoscopy performed due to blood in the stool. It showed diffuse polyps of 0.5-1 cm in the colon and rectum. The pathology was reported as tubular adenoma. He had diffused cafe au lait spots on his body. Brain MRI revealed diffuse gliomas in the

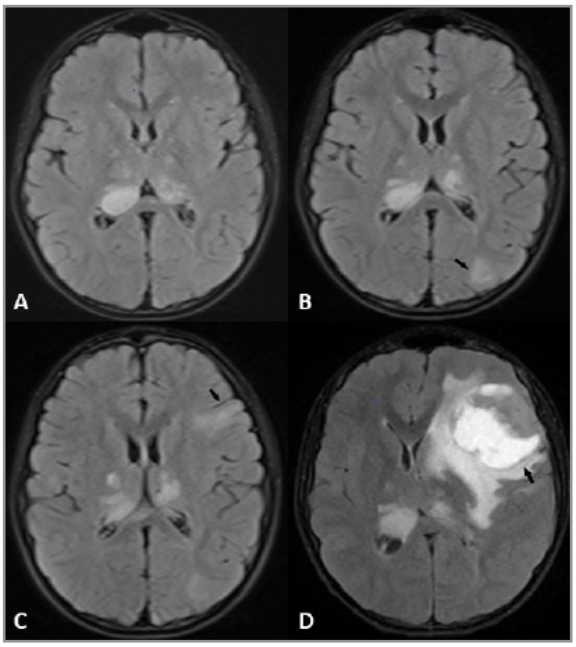

Figure 4. Axial flair brain MRI of patient 5. Hyperintense lesions are seen in bilateral thalamus and basal ganglia **(A)**. The left occipital lesion was revealed (arrow) in addition to the disseminate lesions **(B)** during the treatment and then a new left frontal lesion was revealed (arrow) **(C)**. The left frontal giant mass is seen with surrounding edema and compression effect on midline structures (arrow) after the 30th dose of nivolumab **(D)**.

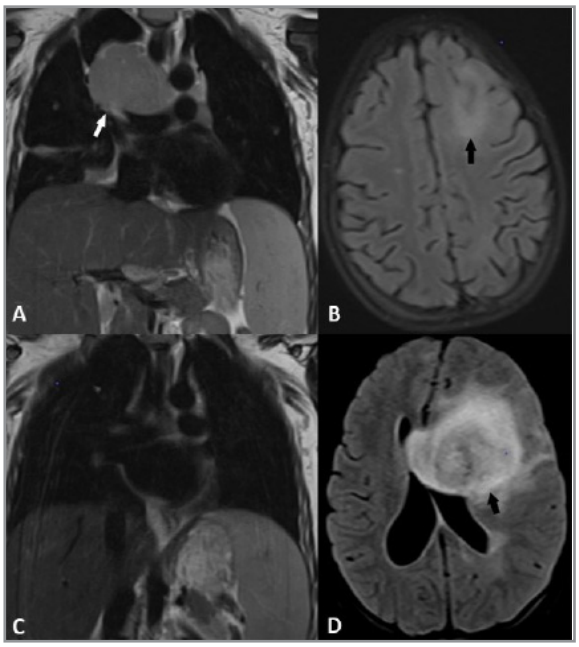

Figure 5. Coronal T2 weighted thorax MRI of patient 7. Mediastinal mass is seen (arrow) **(A)**. Axial flair brain MRI. Hyperintensity in the left frontal lobe (arrow) **(B)**. Mediastinal mass disappeared after 6 doses of R-CHOP (Rituximab+cyclophosphamide+doxorubicin+vincristine+prednizolon) **(C)**. Giant mass in the left frontal lobe with surrounding edema and compression effect on midline structures in brain MRI. (arrow) after 13th dose of nivolumab **(D)**.

basal ganglia and thalamus (Figure 4A). Therefore, he was genetically diagnosed with CMMRD syndrome. Prophylactic nivolumab was initiated due to CMMRD-associated precancerous diffuse gliomas and diffuse tubular adenoma. During the course of nivolumab, MRI revealed new lesions in the occipital and frontal lobes in the CNS (Figures 4B and 4C). At the 17th month (30 doses) of nivolumab, he was admitted to the emergency with seizure. MRI of the brain revealed an almost 8 cm tumor and the pathology was reported as glioblastoma (Figure 4D). Therefore, nivolumab was discontinued. He died about 42 months after beginning nivolumab. There were no drug-related side effects.

Patient 6, a 12-year-old girl diagnosed with H3K27M mutant WHO grade 4 diffuse intrinsic pontine glioma (DIPG). After surgery, temozolomide was given during the radiotherapy. Temozolomide and nivolumab were subsequently initiated concurrently. There were stable findings on MRI after four doses of nivolumab. After six doses of nivolumab, there was progression of the lesion on MRI. One month later, she was admitted with a disturbance in consciousness and was hospitalized in the intensive care unit. Unfortunately, she died about 4 months after beginning of nivolumab. Fatigue and vomiting were observed during the medication.

Patient 7, a 13-year-old girl was diagnosed with T-cell and histiocyte rich, B-cell NHL in the mediastinum (Figure 5A). There was widespread cafe au lait spots on the body. Brain MRI revealed diffuse gliomas in cortical and subcortical areas and hyperintensity in the left frontal lobe (Figure 5B). She was also diagnosed CMMRD syndrome. After six cycles of rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP) chemotherapy, the mediastinal mass disappeared on thoracic MRI (Figure 5C), but pathologic lymph nodes remained on positron emission tomography-computed tomography (PET-CT). Therefore, nivolumab was initiated as monotherapy. While the disease was stable during treatment, she admit-

ted with afebrile seizure at the 6th month of the nivolumab (13 doses) and brain MRI revealed a large tumor in the left frontal lobe (Figure 5D). She was diagnosed with GBM. He died almost 27 months after beginning of nivolumab. There were mild edema and vomiting as an adverse event.

Patient 8, an 8-year-old male was diagnosed with T-cell NHL in the mediastinum and the NHL-BFM 2012 protocol was initiated. He had severe candida sepsis at the induction. Furthermore, he had cafe au lait spots on the body. He was diagnosed with CMMRD syndrome. Since the disease was in remission on MRI before consolidation therapy, nivolumab was initiated as monotherapy. At the end of 6th month (10 doses) of nivolumab, the disease was in remission. Nivolumab could not be continued due to medicine reimbursement problem. The duration after the beginning of nivolumab was almost 31 months and he is in remission currently. No nivolumab-related side effects were observed.

Patient 9, a 17-year-old male was diagnosed with cHL due to a mass in the neck. PET-CT revealed diffuse uptake throughout all body. After six cycles of adriamycin, bleomycin, vincristine, dacarbazine (ABVD), new lesions were detected on PET-CT. Autologous HSCT was performed after three cycles of brentuximab vedotin, ifosfamide, carboplatin, etoposide (BICE). Brentuximab vedotin and nivolumab were initiated concomitantly due to post-transplant residuals. He received six doses of nivolumab and brentuximab vedotin. The duration of follow-up from the initiation of nivolumab until now is 22 months with stable disease. No nivolumab-related side effects were observed.

DISCUSSION

Nivolumab has been shown to be effective in the treatment of adulthood cHL in large case series. In a meta-analysis, they showed that nivolumab is a safe and effective treatment in relapsed/refractory cHL adults.[21] Shen et al. showed that PD-1 or PD-L1 inhibitors as a second line therapy prolonged overall survival in both groups of patients with advanced solid tumors, PD-L1 positive and PD-L1 negative, compared with conventional agents.[22] Nivolumab has shown encouraging results in adults, especially in lymphoma, but data in childhood cancers is very limited.[23] Nevertheless, experience with the use of nivolumab in pediatric cancers has been increasing currently.[24] We observed encouraging outcomes with nivolumab in cHL, immature teratoma and T-LBL, but it failed to prevent glioblastoma progression in children with CMMRD.

The most important marker predicting the efficacy of blockade therapies such as nivolumab, is PD-L1 expression on tumor cells. Childhood tumors with high PD-L1 expression include leukemia (42-100%), lymphomas (27-80%), glioma (75-100%), soft tissue sarcomas (STS) (58%), and metastatic osteosarcoma (75%), and upregulation of PD-L1 was consistently associated with poor clinical outcomes.[15,25]

There have been experiences with nivolumab in various types of pediatric cancer currently. These include histiocytic sarcoma, neuroblastoma, cHL, NHL, germ cell tumors, brain tumors, colorectal carcinoma, MM.[17,26] In a murine model, the combination of anti-PD-1 with blinatumomab has been shown to increase the number of T lymphocytes, which decreased with blinatumomab, and to have a better anti-tumor effect.[27] The combination of nivolumab, ipilimumab and azacitidine was used in a pediatric acute myeloid leukemia (AML) case. It was shown to prolong the remission period and no severe side effects were observed.[28] In this cohort, nivolumab was utilized for NHL, cHL, CNS, germ cell and GIS cancers.

Dilly-Feldis et al. demonstrated that PD-1 expression was low on T lymphocytes, while PD-L1 expression was high on surface of tumor cells in childhood cHL.[29] Davis et al. reported that in a pediatric HL cohort with nine children, tumor cells expressed PD-L1 at levels ranging from 30% to 100%. Moreover, only 15% of tumor cells in the non-lymphoma cohort were shown to express PD-L1. In our cohort, only one patient was diagnosed with cHL. The patient received six doses of nivolumab in combination with brentuximab vedotin after autologous HSCT and is being followed with stable disease.

No objective response was observed in any of the pediatric cancer types except cHL. Children and young adults enrolled in the Children's Oncology Group study (ADVL1412) between 2015 and

2018, had identified that high expression of PD-L1 and high tumor mutation burden correlated with response to IC inhibitors.[30] A low frequency of PD-L1 expression was established among pediatric solid tumors and poor prognostic subtypes were more likely shown to express PD-L1.[31] Ehlert et al. combined dinutuximab with nivolumab in two neuroblastoma patients who were refractory to conventional therapies. They achieved complete remission in one and partial response in the other.[32] Que Y et al. used PD-1 blockade (sintilimab and toripalimab) as monotherapy in nine pediatric cancer patients (HL (6), Burkitt lymphoma (1) and MM (2)) and achieved objective response in 5/6.[33]

Although nivolumab is often used as monotherapy, it has been used in combination with another immunologic agent or a chemotherapy regimen in some types of cancer with encouraging outcomes.[34] The most relevant concern in this regard is that since nivolumab stimulates T cells to attack cancer cells, the use of nivolumab in combination with highly myelosuppressive and immunosuppressive chemotherapies may reduce the effect of the drug. Therefore, maximizing the effect of immune activation while reducing the inhibition of chemotherapeutic drugs on the immune system should be the focus in combination chemotherapy with immunotherapy.[35] In our cohort, we combined nivolumab with temozolomide in patient 6 and with brentuximab in patient 9. In the remaining patients, we preferred to use monotherapy because of refractoriness and many chemotherapeutic agents had been utilized previously.

Cacciotti et al. investigated the efficacy of PD-1 (nivolumab and/or pembrolizumab) and CTLA-4 (ipilimumab) blockade therapies in recurrent and refractory CNS cancers. This study demonstrated that IC inhibitors are safe and effective in the treatment of relapsed/refractory childhood CNS tumors. The longest duration in both DMG and DIPG was 16.2 months and 2.6 months, respectively, although there is lacking data about their efficacy.[36] In this cohort, DMG and DIPG patients were followed up for 6 months and 3 months with stable disease, respectively. A randomized controlled phase III trial failed to demonstrate any superiority of nivolumab over bevacizumab in recurrent glioblastoma.[37] In the CheckMate 908 study, median progression free survival (PFS) in children with high grade glioma who received nivolumab was 1.7 months.[19] While nivolumab did not prevent development of glioblastoma in our two patients with CMMRD syndrome, Sherman et al. demonstrated a stable course for more than 5 years in a 57-year-old woman with Lynch syndrome and glioblastoma.[38] In other pediatric case series of glioblastoma with CMMRD syndrome, AlHarbi[39] reported a PFS of 9 months, Larouche[40] 11 months and Bouffet[41] 5 and 9 months. Gorsi et al. emphasized that PD-L1 expression on tumor cells is important for the efficacy of nivolumab in pediatric CNS cancers.[42] Heynckes et al. showed that temozolomide significantly reduced PD-L1 expression and nivolumab was ineffective.[43] The lack of PD-L1 expression in medulloblastoma indicates a limited effect for immunotherapy with PD1/PD-L1 blockers.[44]

Evidence regarding the use of nivolumab in germ cell tumors is mostly limited in childhood. Nivolumab seems to be efficient and safe in the treatment of adulthood germ cell cancer.[45,46] Zhang et al. showed that PD-1/PD-L1 expression was low and CTLA-4 expression was high in adult testicular yolk sac tumor sites.[47] Although PD-L1 expression is lower in extracranial germ cell tumors, Wildeman et al. have demonstrated that 90% of CNS germinomas have PD-L1 expression.[48,49] Platinum refractory germ cell tumors are very challenging to manage. There have been case reports showing that nivolumab is successful for these patients.[50-52] In this cohort, nivolumab achieved two months PFS in yolk sac tumor but about four years PFS in immature teratoma.

Despite the promising efficacy of all IC inhibitors, immune-related adverse events are still a major concern. Cytokine releasing syndrome (CRS) is a condition of immune hyperactivation identified in cellular and bispecific T-cell immunotherapy. PD-1 receptor blockade is an approach to anti-tumor immune system stimulation. A 29-year-old woman with alveolar soft tissue sarcoma developed severe CRS during nivolumab therapy.[53]

Immune-associated cardiotoxicity, which is rare but can be fatal. Cardiotoxicities such as myocarditis, cardiomyopathy, cardiac fibrosis, heart block and cardiac arrest have been reported. Myocarditis is often accompanied by dysrhythmia.[54] While

hypothyroidism and hyperthyroidism are the most common endocrine complications (Shang YH), other adverse events attribute to nivolumab are type-1 diabetes, lichen planus, neurological complications and cerebral edema.[55-59]

One of the worrying side effects of nivolumab is GVHD, which is highly predicted to develop after allogeneic HSCT. Boekstegers et al. showed that a pediatric T-ALL case developed fatal GVHD during nivolumab use after allogeneic transplantation.[60] Shad et al. safely used nivolumab after haploidentical HSCT in a patient diagnosed leukemia without increasing GVHD.[61] Ito et al. showed that immune-related side effects were more common when PD-1 inhibitor therapy was given before and after allogeneic HSCT in adult lymphoma.[62]

Our report has some limitations. We could not perform molecular studies such as PD-L1 expression on tumor cells and PD-1 expression on T cells. Other limitations include the small number of cases, lack of a controlled group, being retrospective study and short follow-up period.

In summary, lymphoma and brain tumor were the most common in our patients with CMMRD syndrome, and this result was similar to the knowledge in the literature.[63] Our experience with nivolumab in various pediatric cancer types revealed that nivolumab was more effective in patients with lymphoma and immature teratoma. In addition, nivolumab did not prevent the development of glioblastoma in patients with CMMRD. Nivolumab provided PFS of almost 46 months, 22 months, and 31 months in patients with immature teratoma, HL and T-LBL, respectively. There was no significant adverse event attributed to nivolumab except one patient who developed severe generalized edema. Although the data on the use of nivolumab in childhood cancers is scarce, it is concluded that it may be effective in hematological malignancies such as lymphoma and some solid tumors. Further studies are needed to provide more reliable interpretations.

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Correspondence:

Dr. Ekrem UNAL

Hasan Kalyoncu Universitesi, Tip Fakultesi

Pediatri Anabilim Dali

Pediatrik Hematoloji-Onkoloji Bolumu

Sahinbey

GAZIANTEP / TURKIYE

Tel: (+90-545) 486 96 00

e-mail: drekremunal@yahoo.com.tr

ekrem.unal@hku.edu.tr

ORCIDs:

Veysel Gok	0000-0002-7195-2688
Firdevs Aydin	0000-0003-3126-1521
Alper Ozcan	0000-0002-6100-1205
Zehra Filiz Karaman	0000-0003-4552-8098
Ebru Yilmaz	0000-0003-4802-0986
Orhan Gorukmez	0000-0002-9241-0896
Ozlem Gorukmez	0000-0003-2289-8619
Atil Bilgin	0000-0002-2053-9076
Musa Karakukcu	0000-0003-2015-3541
Turkan Patiroglu	0000-0003-2471-764X
Ekrem Unal	0000-0002-2691-4826