Title

Nivolumab in the Treatment of Recurrent or Refractory Pediatric Brain Tumors: A Single Institutional Experience

Journal

Journal of Pediatric Hematology/Oncology, 41(4)

ISSN

1077-4114

Authors

Gorsi, Hamza S
Malicki, Denise M
Barsan, Valentin
et al.

Publication Date

2019-05-01

DOI

10.1097/mph.0000000000001339

Peer reviewed

Nivolumab in the Treatment of Recurrent or Refractory Pediatric Brain Tumors: A Single Institutional Experience

Hamza S. Gorsi, MD, MPH,† Denise M. Malicki, MD, PhD,†‡ Valentin Barsan, MD,†§ Mark Tumblin, BS,†∥ Lanipua Yeh-Nayre, CPNP,†∥ Mehrzad Milburn, BSN,†∥ Jennifer D. Elster, MD,†∥ and John R. Crawford, MD, MS*†∥*

Summary: Successful use of immune checkpoint inhibitors in a variety of cancers has generated interest in using this approach in pediatric brain tumors. We performed a retrospective review of 10 consecutive children (6 boys, 4 girls; ages, 2 to 17 y), with recurrent or refractory pediatric brain tumors (5 high-grade glioma, 1 low-grade glioma, pineoblastoma, medulloblastoma, ependymoma, and CNS embryonal tumor, NOS) treated at Rady Children's Hospital San Diego from 2015 to 2017 with the immune checkpoint inhibitor nivolumab (3 mg/kg every 2 wk). Eight of 10 patients received prior chemotherapy and 9 radiation therapy. Nine patients had radiographic disease progression (median, 2.5 doses). Median time to progression was 5.5 weeks (1.6 to 24 wk). Three patients (2 with high-grade glioma, 1 with CNS embryonal tumor NOS) showed a partial response to treatment at the primary tumor site and 2 of 3 had progression of metastatic disease. Grade 2 toxicities were observed without dose limiting side effects. Tumor mutation burden (TMB) was low to intermediate (median, 1.3; range, 0 to 6.3). Median survival for PD-L1 positive patients was 13.7 weeks versus 4.2 weeks for PD-L1 negative patients ($\rho = 0.08$) nivolumab was well tolerated in our series of pediatric recurrent brain tumors with some transient partial responses in patients with positive PD-L1 expression and higher TMB. Our findings suggest that the use of immune checkpoint inhibitors in pediatric brain tumor patients should be limited to those with elevated PD-L1 expression and TMB.

Key Words: pediatric brain tumor, immunotherapy, checkpoint inhibitors, checkpoint blockers, nivolumab

(*J Pediatr Hematol Oncol* 2018;00:000–000)

The immune system recognizes cancer cells as foreign because of genetic and epigenetic alterations and mount a T-cell–mediated immune response.[1] The intensity of the immune response is modulated by the balance between the costimulatory and coinhibitory signals (also called immune checkpoints) between Antigen Presenting Cells (APC) and T cells.[2] The immune checkpoints prevent against autoimmunity and exaggerated immune response to foreign antigens. Cancer cells up-regulate expression of immune checkpoints, helping them elude the immune response.[1] Identification of the role of immune checkpoints in cancer immune evasion led to an interest in checkpoint inhibitors for cancer treatment. The B7/CTLA-4 and PD-1/PD-L1 axes are the most extensively studied immune checkpoint pathways in the setting of cancer.[2] They have been used in metastatic melanoma, renal cell carcinoma, and nonsmall cell lung cancer and have shown survival benefits.[3]

The integrity of the blood-brain barrier makes brain parenchyma a relatively immune-privileged environment and brain tumors further suppress T-cell–mediated immunity.[4,5] The checkpoints are thought to be involved in the immune evasion of the brain cancer by regulatory T cells (T-regs) upregulation. Increased T-reg fraction (constitutionally expressing CTLA-4) in the setting of decreased total CD4+ T cells has been reported in high-grade brain tumors.[6–8] Similarly, an immunohistochemistry study showed that 30% to 60% of GBM samples had PDL1 expression and 28% of the tumor infiltrated lymphocyte had PD-L1 expression. Moreover, Patients with high PD-1 and PD-L1 expression had worse outcome among GBM patients.[9,10] The expression of the PD1 and PD-L1 among GBM has led to an interest in using immune check point inhibitors for GBM and other brain tumors.

PD-1 inhibitors have provided survival benefit in melanoma, nonsmall cell lung cancer and renal cell carcinoma,[3] but current clinical literature involving use of checkpoint inhibitors in pediatric and adult brain tumors did not show improved survival.[11,12] Merchant et al[13] reported on the safety of ipilimumab (monoclonal antibody against CTLA-4) in noncentral nervous system (CNS) pediatric solid tumors. We present the first single institutional retrospective case series of the immune checkpoint inhibitor nivolumab in exclusively pediatric patients with recurrent or refractory brain tumors.

MATERIALS AND METHODS

We reviewed 10 consecutive pediatric brain tumors patients treated with nivolumab at Rady Children's Hospital between December 2015 and December 2017. All patients had received and failed multiple standard therapies for their diseases before initiation of nivolumab. Nivolumab intravenous injection (3 mg/kg) every 2 weeks was administered off label for compassionate use. The risks and benefits of off label nivolumab therapy were explained and appropriate institutional consent for treatment was obtained before treatment. Neuroimaging was performed after 4 weeks to evaluate the tumor response or earlier if clinically indicated. Radiographic response was ascertained by pediatric neuroradiologist. Clinical response and adverse

Received for publication June 15, 2018; accepted September 24, 2018.
From the Departments of *Neurosciences; ‡Pathology; §Pediatrics; ∥Pediatrics, Division of Hematology Oncology, University of California San Diego, La Jolla; and †Rady Children's Hospital, San Diego, CA.
V.B. is a paid consultant for Illumina. The remaining authors declare that they have nothing to disclose.
Reprints: Hamza S. Gorsi, MD, MPH, ORCID 0000-0002-1136-8543, Rady Children's Hospital, MC 5009, 3020 Children's Way, San Diego, CA 92123 (e-mails: hamzagorsi@gmail.com; hgorsi@ucsd.edu).

events were evaluated every 2 weeks by the treating pediatric neurooncologist at the time of clinic visit. Laboratory evaluations including complete blood count with differential, liver function enzymes, comprehensive metabolic panel, urinalysis, and urine pregnancy in patients of child bearing age were performed before initiation of therapy. Adverse events were categorized according to Common Terminology Criteria for Adverse Events Volume 4.0. Nivolumab was discontinued for those patients with either clinical or radiographic disease progression or at the request of the family. Patients with a stable or responsive disease continued nivolumab until time of progression. PD-L1 expression was assessed by immunohistochemistry at University of California San Diego using Ventana PD-L1 (SP263) Assay. Tumor cells were classified via the following PD-L1 scoring algorithm: high positive ($\geq 50\%$ of tumor cells are positive) positive (25% to 49% of tumor cells are positive), low positive (1% to 24% of tumor cells are positive), and negative ($< 1\%$ of tumor cells are positive). Tumor infiltrative immune cells were classified by the following PD-LI scoring algorithm: positive ($\geq 25\%$ of immune cells positive), negative ($< 25\%$ of immune cells positive), and tumor-associated immune cells absent. Patients received nivolumab irrespective of PD-L1 tumor expression status. Tumor mutation burden (TMB) was derived from the Foundation One CDx results by measuring the total number of somatic mutations (TMB) as a proxy for neoantigen burden.[14] If a patient had multiple surgeries/biopsies, TMB and PD-L1 expression status was calculated from the last pathologic sample obtained before nivolumab treatment. But rebiopsy at the time of the disease progression/relapse was not performed for all the patients. Kaplan Meier Survival was performed using Graphpad Prism Version 7, GraphPad Software, La Jolla, CA. The retrospective review was approved by the University of California San Diego Institutional Review Board.

RESULTS

The demographic and treatment characteristics of 10 patients (6 boys, 4 girls) treated with nivolumab is shown in Table 1. The median age at the time of first dose of nivolumab was 12.5 years (range, 2 to 17 y). Five had high-grade glioma, and one each had low-grade glioma, pineoblastoma, CNS embryonal tumor NOS, ependymoma, and medulloblastoma. One patient with diffuse leptomeningeal CNS embryonal tumor NOS had biopsy only at presentation, whereas the other patients had subtotal (3), near total (2) or gross total resection (4) at presentation. All patients had received standard of care therapy before initiation of nivolumab (Table 2). Nine patients had received radiation therapy (5 focal and 4 craniospinal) before nivolumab, whereas 8 patients had previously received tumor-directed systemic chemotherapy. The total number of doses of nivolumab given was 40, median 2.5 (range, 1 to 12), whereas the median for patients with high-grade glioma was 4.5 (range, 2 to 12). Nine patients eventually died of disease progression (only patient 8 was alive at the time of data collection) and 9 of these 10 patients progressed while on nivolumab. The median time to progression was 5.5 weeks (range, 1.6 to 24). Three patients (patient number 1, 3, and 4) had radiographic response to nivolumab (Table 2; Fig. 1). Patient 1 had disease only in her brain, and she showed radiographic responded to the treatment, but family opted to withhold further treatment in spite of disease response because of poor quality of life and she died shortly after discontinuation of nivolumab. Patient 3 continued to show radiologic improvement in the brain MRI, with worsening of spinal dissemination resulting in discontinuation of therapy after 7 doses. Primary brain disease for patient 4 showed radiologic response to nivolumab, but he developed progressive bony metastatic lesions in spine, and nivolumab was discontinued after 6 doses.

TABLE 1. Demographic and Treatment Characteristics of Patients Treated With Nivolumab

Demographic or Treatment Variable	All Patients
Age at initial Diagnosis [median (range)]	11 y (1.5-17)
Age at time of Nivolumab [median (range)]	12.5 (2-17)
Sex	
Male	6
Female	4
Diagnosis	
High-grade glioma	5
Low-grade glioma	1
Pineoblastoma	1
CNS embryonal tumor, NOS	1
Medulloblastoma	1
Ependymoma	1
Prior chemotherapy	
Yes	8
No	2
Prior surgery	
Gross total resection	4
Near total resection	2
Subtotal resection	3
Biopsy	1
Prior radiation	
Yes	9
No	1
No. doses	
Total	40
Median	2.5
Range	1-12
Time to progression [median (range)]	
Entire cohort	5.5 wk (1.6-24)
PD-L1 positive	13.7 wk (4.6-24)
PD-L1 negative	4.2 wk(1.6-6.6)
PD-L1 status	
Positive	3
Negative	6
Unknown	1
Tumor mutation burden	
Low	5
Intermediate	1
High	0
Not available	4

Tumor molecular analysis was performed for each patient as shown in Table 2. Tumor mutation burden (TMB) was calculated in 6 of 10 patients and was low to intermediate (mean, 2; median, 1.3; range, 0 to 6.3). PD-L1 expression status was assessed in 9 patients (3 low positive, 6 negative) as shown in Fig. 2. Tumor infiltrative immune cells were absent in each of the tumors analyzed for PD-L1 expression. Median time to progression varied depending on PD-L1 expression status. PD-L1 positive patients had progression at 13.7 weeks (mean, 14.1; range, 4.6 to 24), whereas PD-L1 negative patients had a median progression at 4.2 weeks (mean, 4.1; range, 1.6 to 6.6); however, it did not reach statistical significance ($P = 0.088$) (Fig. 3).

One patient with the highest TMB (6.3) in our series with GBM had shown radiographic response on nivolumab

TABLE 2. Treatment Characteristics of Individual Patient Treated With Nivolumab

Number	Demographics Location, Metastasis	Prior Treatment Given	Molecular Features	Tumor Mutation Burden	PD-L1 Status	Doses Given	Radiographic/Clinical Outcome
1	17 y/o female with hemispheric GBM with leptomeningeal metastases	1: XRT and temozolomide 2: Voyager device during Nivolumab	KDR, KIT, PDGFRA amplification CDKN2A/B loss, TP53P278L and R248W, ATRXQ1008 H3F3AG35R	6.3	Low positive	12	Radiographic response until 24 wk then discontinuation of therapy due to parental preference DOD
2	13 y/o female Pineal high-grade glioma and extra CNS bony metastatic lesions	1: XRT, carbo & VCN 2: CCNU and temozolomide	NF1, ATRX, FGFR1, H3F3A. gain of 1q, 12q, 16p, loss of 3p, 4q, 10p, 10q, 11q, 18p, 18 q, xq, chromothripsis chromosome 4q and 12q	NA	Low positive	2	Progression after 4.6 wk DOD
3	14 y/o female with primary leptomeningeal CNS embryonal tumor, NOS	1: XRT, carbo & VCN 2: Everolimus & Trametinib	AKT3, ATMR457, IKBKE, IRS2, MCL1, FGF14, GABRA6T113M, MDM4, NOTCH2, PIK3C2B, BRAFKiAA1549-BRAF fusion	2.7	QNS	7	Radiographic response of brain disease, stable spinal dissemination. Progression after 20 wk DOD
4	12 y/o male with midline high-grade glioma with leptomeningeal and bony metastases	1: XRT	H3F3A K28M [aka K27M] mutation, TP53 R273C mutation, amplifications of KIT, KDR, PDGFRA, CHIC2, and high copy gains of CCND1, FIP1L1 (x5)	NA	Low positive	6	Radiographic response of brain disease, worsening bony metastatic lesions at 13.7 wk DOD
5	13 y/o male with supra-tentorial anaplastic ependymoma with leptomeningeal metastases	1: XRT	NF1, CDKN2A	1.8	Negative	2	Progression at 5.7 wk DOD
6	2 y/o male with Pineoblastoma and leptomeningeal metastases	1: XRT, VCN, cyclophosphamide, methotrexate, cisplatin	DICER1, PTCH1 mutation, gains of 2p/ proximal 2q, distal 3q, and proximal 5p	NA	Negative	1	Progression at 1.56 wk DOD
7	16 y/o male with secondary hemispheric GBM 13 y after treatment for Medulloblastoma	1: CCNU,Temozolamide for GBM, 2: XRT, cyclophosphamide, cisplatin, VCN, etoposide for medulloblastoma 3: XRT+ Temozolomide, carboplatin Cyclophosphamide, HDC+SCR +RA for relapsed medulloblastoma	TP53, CDKN2A, CDKN2B, MET	NA	Negative	3	Progression at 6.6 wk DOD
8	6 y/o male with low-grade astrocytoma of cervical cord with leptomeningeal metastases	1: Avastin 2: carboplatin 3: vinblastine	BRAF KIAA154-BRAF	0.8	Negative	2	Progression at 2.6 wk Alive
9	11 y/o female with medulloblastoma with leptomeningeal metastases	1: XRT, vincristine, cyclophosphamide, cisplatin 2: Avastin, irinotecan, temozolomide 3: Everolimus & vorinostat	KDM6A R519	0	Negative	3	Progression at 5.4 wk DOD
10	7 y/o male hemispheric GBM	1: XRT, Temazolamide 2: Avastin 3: Pablociclib	CCND2, CDK4, MDM2	0.8	Negative	2	Progression at 3 wk DOD

Low positive means 1% to 24% tumor cells are PD-L1 positive.

CCNU indicates lomustine; DOD, died of disease; GBM, glioblastoma multiforme; HDC+SCR+RA, high dose chemotherapy+stem cell rescue+cis-retinoic acid; NA, not applicable; QNS, quantity not sufficient; VCN, vincristine; XRT, radiation therapy.

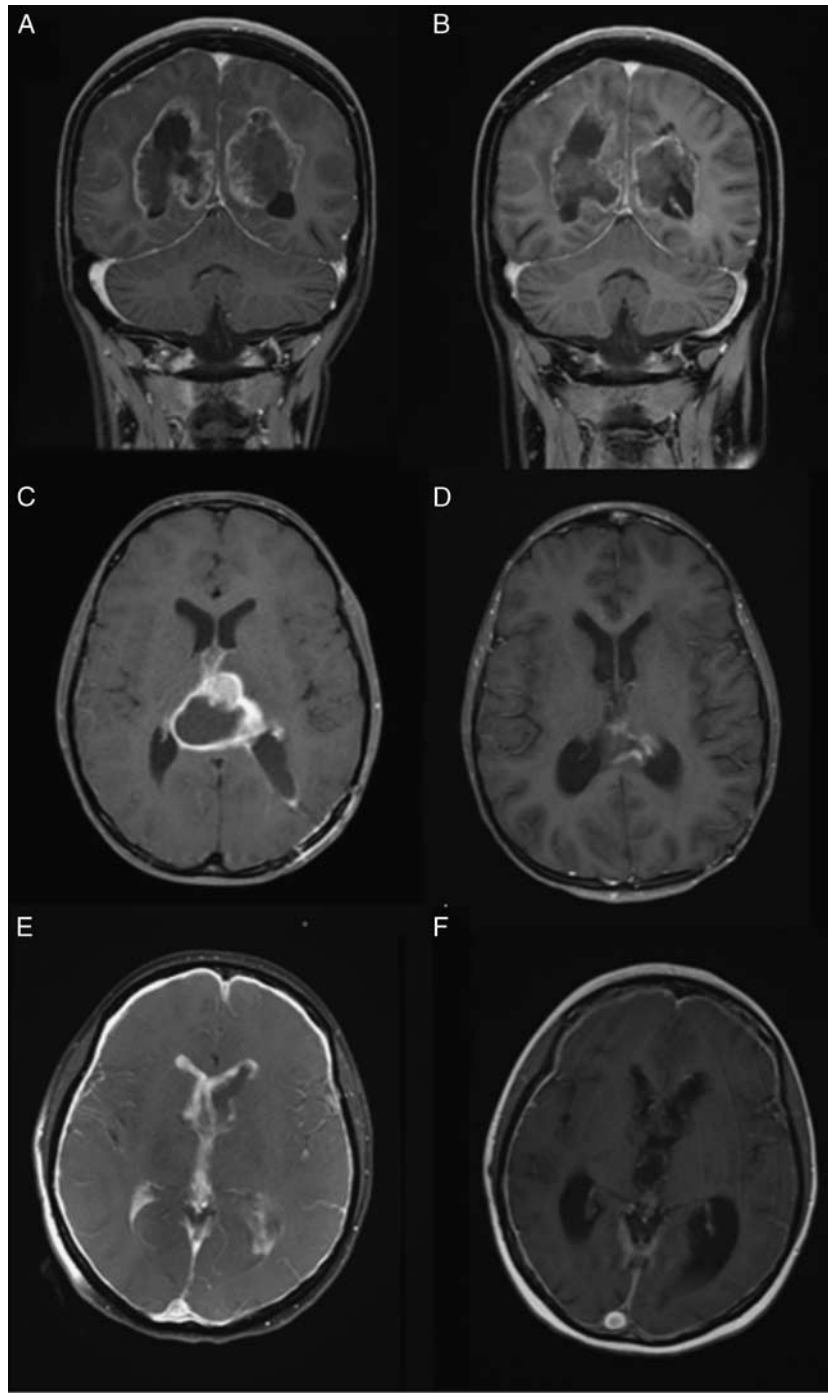

FIGURE 1. T1-Post Gadolinium MRI before and after nivolumab treatment. A, Prenivolumab brain MRI for patient 1; B, decreased disease burden post nivolumab. C, Prenivolumab brain MRI for patient 4; D, shrinking tumor size postnivolumab. E, Prenivolumab brain MRI for patient 3; F, decreased leptomeningeal and ependymal enhancement postnivolumab treatment.

for 24 weeks, longer than any other patients in our series. Although this patient had elevated TMB, there was no evidence of constitutional mismatch repair deficiency or any other known tumor predisposition syndrome and was not exposed to temozolomide before the TMB testing. The 3 remaining patients with GBM had earlier progression (range, 3 to 7.5 wk); however, TMB was only available for 1 of the 3 patients and was calculated to be low (0.8).

Nivolumab was well tolerated without dose limiting toxicities. Grade 2 adverse events included leukopenia (3), transaiminitis (1), hyperglycemia (1), hypoalbuminemia (1), pancreatitis (1), anemia (1), nausea/vomiting (1), and thrombocytopenia (1). One family withheld treatment because of poor general quality of life, confusion, and memory loss associated with disease. One patient had delayed dosing of 1 week because of subclinical pancreatitis

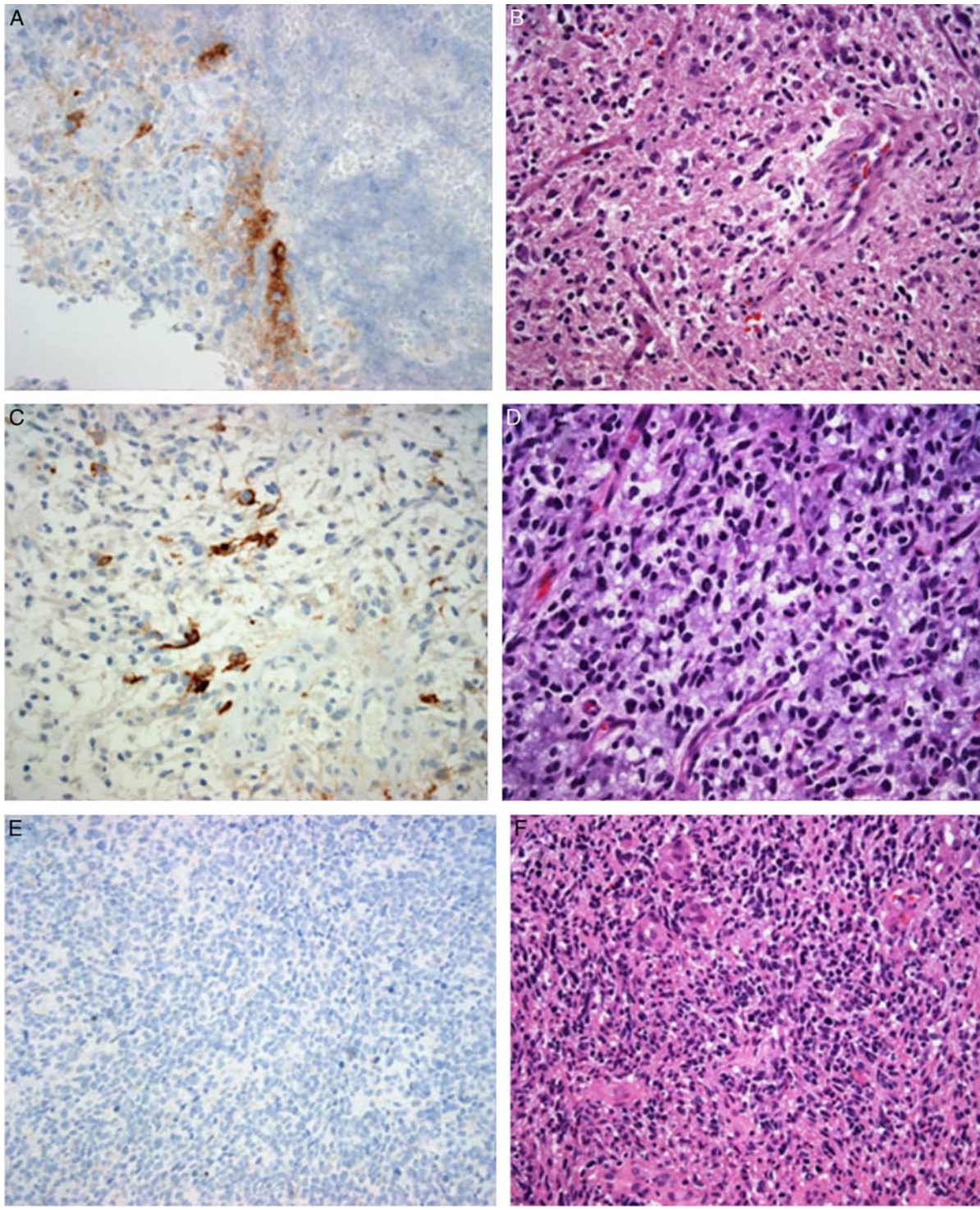

FIGURE 2. Representative PD-L1 immune histochemical expression and hematoxylin-eosin staining. A, PD-L1 IHC expression for patient 1 (PD-L1 status+ve); C, PD-L1 IHC expression for patient 4(PD-L1 status +ve); E, PD-L1 IHC expression for patient 10 (PD-L1 status –ve). B, D, and F, H&E staining for patient 1 (glioblastoma multiforme), 4 (high-grade glioma), and 10 (glioblastoma multiforme), respectively (×40 magnification). Samples with ≥1% of cells staining for membranous PD-L1 are considered PD-L1 positive. full color online

(patient 1). One patient (patient 3) had several dosing delays unrelated to medication (shunt malfunction and parental preference). All adverse effects were short lived and resolved within 2 weeks after discontinuation.

DISCUSSION

Tumor cells can evade immune-mediated destruction by multiple mechanisms, including activation of immune checkpoints. Clinical trials have shown an improved survival outcome

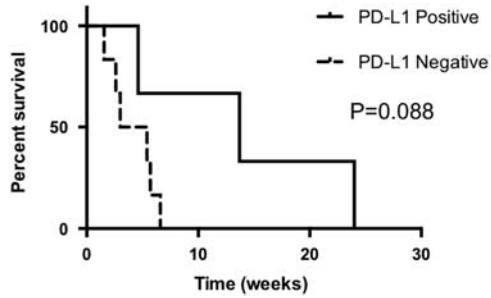

FIGURE 3. Kaplan-Meier survival curve comparing progressions free survival. PD-L1 positive patients have longer survival (median, 13.7 wk) compared with PD-L1 negative patient (median, 4.2 wk), but this difference did not reach statistical significance ($P = 0.08$).

in cancers with up-regulated immune checkpoints, including nonsmall cell lung cancer, renal cell carcinoma and metastatic melanoma if treated with checkpoint inhibitors.[3] Up regulation of immune check points in brain tumor cells has resulted in high interest in immune checkpoint inhibitors in CNS tumors. Our limited experience shows that among pediatric patients with recurrent/refractory brain tumor who failed standard treatment, nivolumab was well tolerated without any serious dose limiting side effects. Unrestrained immune response because of checkpoint blockade leads to immune-mediated adverse events like colitis, hypophysitis, vitiligo, pancreatitis and transaminitis,[2] and patients with grade 2 or higher immune-mediated adverse events have been shown to have longer overall survival compared with those with grade 1 or less adverse events.[15] In our series, patient 1 showing the best response to nivolumab had developed grade 2 acute pancreatitis during the treatment course, requiring dosing delays. Three patients had transient partial response, whereas 9 patients eventually progressed while on nivolumab. Median time to disease progression was 5.5 weeks (range, 1.6 to 24 wk).

Tumor mutation burden is a marker for the response to immune check point inhibitors, that is, patients with higher mutation burden respond better to immune check point inhibitors compared with those with low mutation burden.[16] Tumor mutation burden of patients in our series was low to intermediate (median, 1.3; range, 0 to 6.3), which is consistent with previously reported low tumor mutation burden in pediatric brain tumors.[17] Pediatric GBM with mismatch repair defects (and hence high TMB) have previously shown response to checkpoint inhibitors.[18] Although our patients with GBM and elevated TMB did not have evidence of constitutional mismatch repair deficiency or any other known tumor predisposition syndrome; one of them had intermediate TMB (6.3 mutations/MB), and showed radiologic response to nivolumab for 24 weeks, the longest in our series.

Although clinical trials have shown a correlation between the PD-L1 expression on lung cancer cells and their response to the PD-L1 inhibitors,[19] a small fraction of PD-L1 negative cells have shown some response to PD-L1 inhibitors.[20] Thus, we did not restrict nivolumab to the patients expressing PD-L1. Limiting the nivolumab infusion only to the patients expressing PD-L1 may give a better estimate of the effect of the nivolumab in pediatric brain tumors. However, in the absence of any other viable option, nivolumab use may be feasible in PD-LI negative patients.

In our series, the median time to progression on nivolumab for PD-L1 positive patients was 13.7 weeks, as compared with 4.2 weeks for PD-L1 negative patients ($\rho = 0.08$). The effects of PD-L1 expression on survival in pediatric brain tumors has been recently reported by a number of groups and shows considerable variability depending on tumor type.[7,21–23] Larger clinical trials are needed to further explore this relationship, as our findings did not achieve statistical significance, possibly because of the small number of patients studied or lack of uniform diagnosis.

Nivolumab was discontinued in <6 weeks because of the radiographic evidence of disease progression in 6 patients, without making a distinction between true progression and pseudoprogression.[15–24] Five of these patients died shortly after discontinuation of the treatment, favoring true disease progression in those patients. Future studies involving checkpoint blockers should account for pseudoprogression in the disease evaluation and consider continuing the treatment despite radiographic evidence of progression early on, if patient remains clinically stable.[25]

This publication has several limitations. It is a retrospective series review and may have selection bias and information bias. This is a relatively small case series, with no standardization of patient selection criteria in terms of histologic diagnosis or molecular features and patients received nivolumab irrespective of their TMB status. Based upon the complexity of the imaging with an admixture of bulk and leptomeningeal disease it was not always possible to quantify the exact treatment response in terms of size or to differentiate progression from pseudoprogression. Further prospective multi-institutional clinical trials with more rigorous inclusion criteria which may involve TMB status and PD-L1 expression status are needed to demonstrate safety and efficacy of nivolumab in the management of either newly diagnosed or recurrent/refractory pediatric brain tumors.

All patients in our series had high risk disease that was refractory to standard therapies including chemotherapy and in most cases radiation therapy before the off-label use of nivolumab. The ability to use off label therapies in pediatric cancer is highly individualized depending on governmental regulations and must include informed consent. In our series, this was deemed appropriate as there were no other effective treatments available and informed consent was obtained before initiation of therapy.

Our limited experience in a variety of progressive pediatric brain tumors provides some early data about the safety of nivolumab in pediatric brain tumors and disease response in some cases, but no firm conclusions can be drawn about its safety or efficacy. Future clinical trials stratifying for TMB in association with tumor subtype and PD-L1 expression status may be necessary to demonstrate potential efficacy of PD-L1 inhibitors in recurrent pediatric brain tumors.

CONCLUSIONS

Nivolumab was well tolerated in our series of pediatric patients with recurrent brain tumors with some transient partial responses. Our findings suggest that the use of immune checkpoint inhibitors in pediatric brain tumor patients should be limited to those with elevated PD-L1 expression and TMB.

ACKNOWLEDGMENTS

This work was supported by the Gordon Fellowship in Pediatric Neuro-Oncology Celebrating Futures Fund.

REFERENCES

1. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12:252–264.

2. Kim JE, Lim M. The role of checkpoints in the treatment of GBM. *J Neurooncol*. 2015;123:413–423.
3. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma. *N Engl J Med*. 2015;373:1803–1813.
4. Harling-Berg CJ, Park TJ, Knopf PM. Role of the cervical lymphatics in the Th2-type hierarchy of CNS immune regulation. *J Neuroimmunol*. 1999;101:111–127.
5. Raychaudhuri B, Rayman P, Ireland J, et al. Myeloid-derived suppressor cell accumulation and function in patients with newly diagnosed glioblastoma. *Neuro-oncology*. 2011;13:591–599.
6. Fecci PE, Mitchell DA, Whitesides JF, et al. Increased regulatory T-cell fraction amidst a diminished CD4 compartment explains cellular immune defects in patients with malignant glioma. *Cancer Res*. 2006;66:3294–3302.
7. Witt DA, Donson AM, Amani V, et al. Specific expression of PD-L1 in RELA-fusion supratentorial ependymoma: Implications for PD-1-targeted therapy. *Pediatr Blood Cancer*. 2018;65: e26960.
8. Plant AS, Koyama S, Sinai C, et al. Immunophenotyping of pediatric brain tumors: correlating immune infiltrate with histology, mutational load, and survival and assessing clonal T cell response. *J Neurooncol*. 2018;137:269–278.
9. Nduom EK, Wei J, Yaghi NK, et al. PD- L1 expression and prognostic impact in glioblastoma. *Neuro Oncol*. 2016;18: 195–205.
10. Majzner RG, Simon JS, Grosso JF, et al. Assessment of programmed death ligand 1 expression and tumor associated immune cells in pediatric cancer tissues. *Cancer*. 2017;123: 3807–3815.
11. Blumenthal DT, Yalon M, Vainer GW, et al. Pembrolizumab: first experience with recurrent primary central nervous system (CNS) tumors. *J Neurooncol*. 2016;129:453–460.
12. Reardon ADA, Omuro AA, Brandes J, et al. OS10.3 randomized phase 3 study evaluating the efficacy and safety of nivolumab vs bevacizumab in patients with recurrent glioblastoma: CheckMate 143. *Neurooncology*. 2017;19(suppl 3):iii21–iii22.
13. Merchant MS, Wright M, Baird K, et al. Phase I clinical trial of ipilimumab in pediatric patients with advanced solid tumors. *Clin Cancer Res*. 2016;22:1364–1370.
14. Johnson DB, Frampton GM, Rioth MJ, et al. Targeted next generation sequencing identifies markers of response to PD-1 blockade. *Cancer Immunol Res*. 2016;4:959–967.
15. Antonios JP, Soto H, Everson RG, et al. Detection of immune responses after immunotherapy in glioblastoma using PET and MRI. *Proc Natl Acad Sci USA*. 2017;114:10220–10225.
16. Teng F, Meng X, Kong L, et al. Progress and challenges of predictive biomarkers of anti PD-1/PD-L1 immunotherapy: a systematic review. *Cancer Lett*. 2018;414:166–173.
17. Vogelstein B, Papadopoulos N. Cancer genome landscapes. *Science*. 2013;339:1546–1558.
18. Bouffet E, Larouche V, Campbell BB, et al. Immune checkpoint inhibition for hypermutant glioblastoma multiforme resulting from germline biallelic mismatch repair deficiency. *J Clin Oncol*. 2016;34:2206–2211.
19. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus Docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373:1627–1639.
20. Mino-Kenudson M. Programmed cell death ligand-1 (PD-L1) expression by immunohistochemistry: could it be predictive and/or prognostic in non-small cell lung cancer? *Cancer Biol Med*. 2016;13:157–170.
21. Hwang K, Koh EJ, Choi EJ, et al. PD-1/PD-L1 and immune-related gene expression pattern in pediatric malignant brain tumors: clinical correlation with survival data in Korean population. *J Neurooncol*. 2018;139:281–291.
22. Zeng J, Zhang XK, Chen HD, et al. Expression of programmed cell death-ligand 1 and its correlation with clinical outcomes in gliomas. *Oncotarget*. 2016;7:8944–8955.
23. Vermeulen JF, Van Hecke W, Adriaansen EJM, et al. Prognostic relevance of tumor-infiltrating lymphocytes and immune checkpoints in pediatric medulloblastoma. *Oncoimmunology*. 2017;7:e1398877.
24. Qin L, Li X, Stroiney A, et al. Advanced MRI assessment to predict benefit of anti-programmed cell death 1 protein immunotherapy response in patients with recurrent glioblastoma. *Neuroradiology*. 2017;59:135–145.
25. Okada H, Weller M, Huang R, et al. Immunotherapy response assessment in neuro-oncology (iRANO): a report of the RANO working group. *Lancet Oncol*. 2015;16:e534–e542.