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Journal

Journal of Neuro-Oncology, 140(3)

ISSN

0167-594X

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Publication Date

2018-12-01

DOI

10.1007/s11060-018-2991-5

Peer reviewed

Journal of Neuro-Oncology
https://doi.org/10.1007/s11060-018-2991-5

CLINICAL STUDY

Reirradiation and PD-1 inhibition with nivolumab for the treatment of recurrent diffuse intrinsic pontine glioma: a single-institution experience

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Received: 14 May 2018 / Accepted: 27 August 2018

Abstract

Background Diffuse intrinsic pontine glioma (DIPG) is a rare, aggressive brain tumor with no known cure. Reirradiation (reRT) at recurrence can prolong survival. The impact of irradiation may be heightened when combined with PD-1 inhibition. We describe our experience using reRT, with or without PD-1 inhibition, in a cohort of patients with recurrent DIPG.

Methods We performed a retrospective cohort analysis of children who received reRT with or without concomitant PD-1 inhibition for recurrent DIPG at a single institution between 2005 and 2016. We compared progression-free (PFS) and overall survival (OS) between those who received reRT alone or in combination with PD-1 inhibition. We then compared reRT to a cohort of patients who did not receive reRT.

Results Thirty-one patients were included (8—reRT with nivolumab; 4—reRT alone; 19—no reRT). Patients who received reRT had prolonged OS compared to no reRT (22.9 months—reRT with nivolumab; 20.4 months—reRT alone; 8.3 months—no reRT; $p < 0.0001$). Patients who received reRT with nivolumab vs. reRT only had slightly prolonged OS from diagnosis and from reRT (22.9 vs. 20.4 months for time from diagnosis; 6.8 vs. 6.0 months for time from reRT). All patients receiving reRT with or without nivolumab tolerated the therapy without acute or late toxicity.

Conclusions Our experience demonstrates the tolerability of reRT with concurrent PD-1 inhibition for recurrent DIPG and suggests that combination therapy may offer survival benefit. Future prospective studies are needed to confirm the benefits of this combination therapy.

Keywords DIPG · Reirradiation · PD-1 inhibition · Survival

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a uniformly lethal pediatric malignancy with a median survival of only 10 months, despite decades of therapeutic trials [1–7].

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Published online: 11 September 2018

Radiation therapy (RT) is currently the only established life-prolonging therapy [6, 8–11], with chemotherapy and targeted therapeutics showing no added efficacy [7]. DIPG typically progresses locally, although loco-regional and distal metastasis can occur [2, 3, 12–14]. Pharmacologic therapies in the recurrent setting are generally ineffective and characterized by rapid neurological decline with median overall survival (OS) of 1 to 4 months following recurrence [7, 15]. Reirradiation (reRT) at the time of disease progression and tumor recurrence has demonstrated improved survival, with an average of about 3 months added to OS when compared to patients receiving upfront radiation only [16].

Recent pre-clinical evidence suggests that activation of the programmed cell death (PD-1) pathway within the tumor microenvironment plays a role in the pathogenesis of adult and pediatric high-grade gliomas [17–22]. In murine glioma models, PD-1 blockade prolongs survival and leads to durable responses [23, 24]. Other pre-clinical studies have suggested PD-1 inhibition combined with radiation therapy offers added survival benefit, potentially through increased antigen presentation and lymphocyte concentration [25, 26]. These findings, combined with recent trials demonstrating success of immune-blockade for the treatment of brain metastases, have led to the testing of PD-1 inhibitors for the treatment of recurrent DIPG (NCT02359565) [27–29]. Additionally, a recent retrospective cohort analysis of nine patients with newly diagnosed DIPG demonstrated a median OS of 15.6 months after combination radiation and PD-1 inhibition with pidilizumab, compared to a median OS of less than one year obtained from historical comparisons [30]. Unfortunately, a recent pediatric trial investigating the use of pembrolizumab for the treatment of recurrent DIPG was modified early on to exclude recurrent DIPG due to severe toxicities that were seen in initial patients [31]. The culmination of these findings supports the need for ongoing investigation of the application of PD-1 inhibition in this patient population.

Nivolumab is an alternative IgG human monoclonal antibody, targeting the PD-1 receptor and blocking interaction with its ligands, PD-L1 and PD-L2. Nivolumab is FDA-approved, appears to have a favorable safety and efficacy profile, and is undergoing investigation for the application in pediatric malignancies (NCT02204458) [19, 32, 33]. Here, we present our single institution's experience using reRT and PD-1 inhibition with nivolumab compared to reRT alone in patients with recurrent DIPG and as compared to those receiving upfront radiation alone, without reRT.

Methods

A retrospective chart review was performed on all patients diagnosed with DIPG between July 1, 2005 and July 31, 2016 at a single academic medical center (University of California, San Francisco). Inclusion criteria included: (1) a diagnosis of DIPG confirmed by either radiographic features and/or biopsy, and (2) initial diagnosis ≤ 18 years of age. Patients were described as those receiving nivolumab combined with reRT, those receiving reRT without nivolumab, or those receiving upfront radiation but without reRT or nivolumab. Interventions were based on evidence of safety and efficacy available and preclinical support for each therapeutic option at time of treatment. Reirradiation was offered in our institution starting in the year 2012, and nivolumab was administered in combination with radiation starting in 2015. Administration of other systemic agents was not an exclusion criteria. Steroid use was not an exclusion criteria for reRT with nivolumab; however, steroids were tapered to the lowest tolerable dose before initiation of nivolumab. Reirradiation occurred no sooner than 6 months from completion of initial radiation. For reRT, the area of recurrent tumor was designated by gross tumor volume (GTV). The GTV was expanded by 1 cm to generate the clinical target volume (CTV), and additional 0.3 cm margin was added to produce the planning target volume (PTV). For the nivolumab cohort, nivolumab was given as a standard dose of 3 mg/kg/dose every 14 days for 28-day cycles. Nivolumab was started concomitantly with radiation and continued as monotherapy after completion of reRT.

Progression-free survival (PFS) was defined as the time interval (months) between the last day of RT or reRT and the date when progression was first identified. All imaging was reviewed at a multidisciplinary pediatric neuro-oncology tumor board consisting of neuroradiologists, neuropathologists, neuro-oncologists, and radiation oncologists. Radiographic progression was determined by increased volume within the tumor and/or T2/FLAIR changes on non-enhancing tumors, consistent with progression and not attributable to radiation treatment effects, as determined by imaging characteristics and time from radiation. Radiographic progression was correlated with clinical symptoms when possible. OS was defined as the time interval (months) between the date of diagnosis to date of death. OS after reRT was defined as the time interval (months) between the last day of reRT and the date of death.

Descriptive statistics were used to compare clinical characteristics between treatment cohorts. The following statistical tests were used: Chi-squared tests for binary variables (sex, completion of biopsy), ANOVA for normally distributed variables (age), non-parametric Kolmogorov–Smirnov or Kruskal–Wallis test for non-normally distributed variables (number of systemic agents received). Survival outcomes were compared using Kaplan–Meier survival (KMS) analysis and significance calculated by log-rank test. Statistical analyses were performed in the statistical environment R (version 3.3.2) with the *survival* package (version 2.41).

Results

A total of 31 patients were included in the cohort (Fig. 1). Of the 31, 12 patients aged 3–18 years were included in the cohort of patients undergoing reRT. Eight of 12 patients received nivolumab in combination with reRT and are henceforth referred to as the "nivolumab + reRT cohort." The remaining 4 patients received reRT alone and are referred as the "reRT cohort." An additional 19 patients aged 2 to 13 years were included in the cohort of patients undergoing radiation at time of diagnosis, without receiving reRT or nivolumab at progression, and are referred as the "RT cohort" (Table 1; Fig. 1). There was no statistically significant difference in age at diagnosis ($p = 0.83$) or sex distribution across all cohorts ($p = 0.22$; Table 2).

In 7 of the 8 patients in the nivolumab + reRT cohort, 2 of the 4 patients in the reRT cohort, and 8 of the 19 RT patients, the diagnosis was confirmed by surgical biopsy (Table 1). One patient (#8), in the nivolumab + reRT group, was re-biopsied at recurrence and confirmed to have progressive DIPG. In the remaining patients, the diagnosis was confirmed based on radiographic criteria alone. There was no statistically significant difference in proportion of patients who received biopsies between the three cohorts; however, a larger proportion received biopsies in the nivolumab + reRT cohort compared to the other two cohorts ($p = 0.09$). Nine of 10 patients who had mutational analyses performed had pathogenic H3 K27M mutations. Five of these patients had H3.3 K27M mutations confirmed by molecular sequencing. There were no confirmed H3.1 K27M mutations noted in the cohort and only one patient had wildtype H3. All patients received between 54.0 and 60.0 Gy following diagnosis with a conventionally fractionated (1.8–2.0 Gy per fraction) radiation plan directed towards the brainstem. Upon disease progression, the 8 patients in the nivolumab + reRT cohort received fractionated reirradiation (24 Gy total; 2–2.4 Gy per fraction) with concurrent and then adjuvant nivolumab. Two patients received a 12 Gy boost (36 Gy total) to areas of disease progression outside of the prior radiation field. Patients received between 1.5 and 6 total cycles of nivolumab (median 3.3 cycles). The 4 patients in the reRT cohort received reirradiation alone (24 Gy total; 2–2.4 Gy per fraction). The median time to reirradiation (defined as end of initial radiation to start of reirradiation) was the same between the nivolumab + reRT and reRT cohorts (11.6 mo [range 7.5–21.6] vs. 12.1 mo [range 9.4–13.3]; $p = 0.90$).

Virtually all of the patients in the cohort (30 of 31) received systemic chemotherapy or other targeted

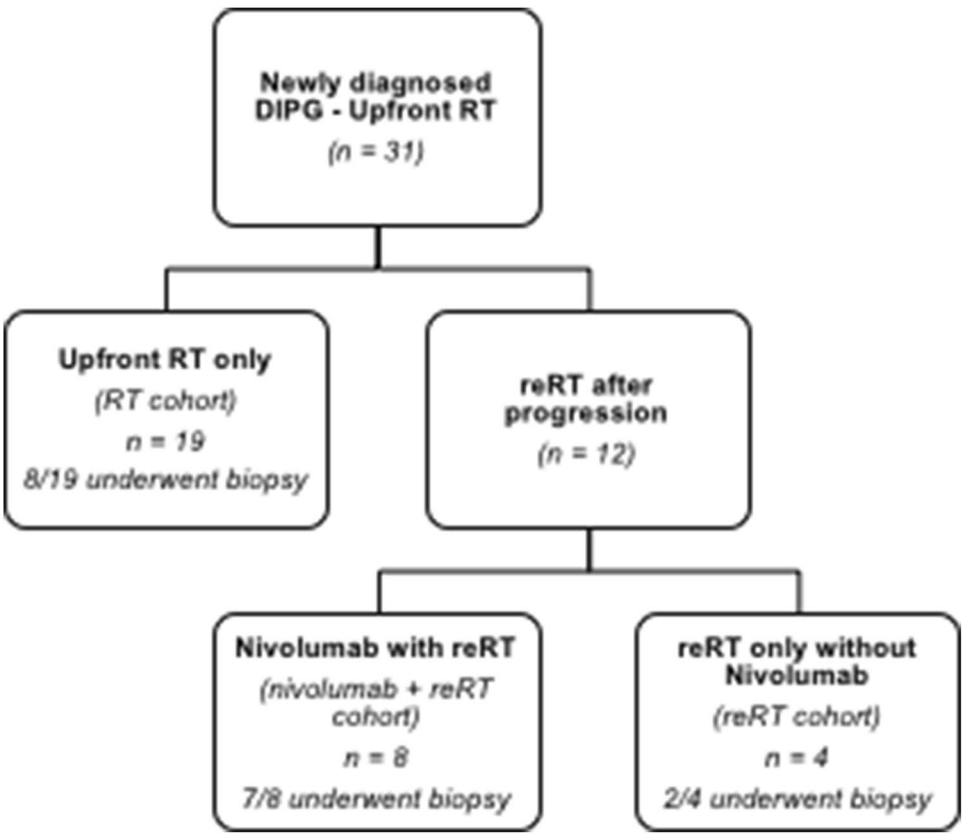

Fig. 1 Schematic of patients in our study, subdivided into treatment cohorts and with associated number of patients within the cohort that underwent biopsy at diagnosis. *RT* radiation therapy, *reRT* reirradiation

Table 1 Diagnostic and treatment details for all patients in the study cohort

Patient #	Age at diagnosis (yrs); Sex	Cohort	Pathology	First -line treatment	Tx at progression (pre-reRT)	Tx at progression (post-reRT)	# of Nivo cycles	Time to ReRT (mo)	OS from initial diagnosis (mo)	OS after reRT (mo)	PFS after first RT (mo)	PFS after reRT (mo)	Initial RT, Gy (frac)	ReRT dose, Gy (frac)
1	18, F	reRT	Astro WHO grade II	Temozolomide	Lomustine Bevacizumab	Sunitinib	-	9.4	14.3	2.8	7.0	0.5	55.8 (31)	24 (12)
2	6, F	reRT	Astro WHO grade III	Capecitabine	(1) VEGFR inhibitor (PTC299) (2) Temozolomide	(1) Erlotinib (2) Etoposide (3) Lapatinib	-	13.3	26.1	10.5	9.3	8.2	55.8 (31)	24 (12)
3	5, F	reRT	None	Capecitabine	Sunitinib	Bevacizumab	-	10.9	20.8	7.5	8.3	4.1	55.8 (31)	24 (12)
4	3, F	reRT	None	Veliparib Temozolomide	CED valproate	None	-	13.3	19.9	4.5	4.2	NA	54 (30)	24 (10)
5	4, F	reRT + nivo	AA WHO grade III, H3K27M	Bevacizumab	(1) Temozolomide combined with PARP inhibitor (2) Panobinostat (3) Nivolumab Bevacizumab	Bevacizumab	5.5	24.2	33.4	6.8	21.3	5.2	59.4 (33)	24 (10)
6	8, M	reRT + nivo	Astro WHO grade III, H3K27M	Adavosertib	Nivolumab	None	5	8.0	16.4	6.1	7.3	2.0	54 (30)	24 (12)
7	4, F	reRT + nivo	Astro WHO grade II, H3.3K27M	Dasatinib Etoposide	Nivolumab	None	3	20.4	28.5	6.0	16.7	3.2	54 (30)	24 (12)
8	13, M	reRT + nivo	DIPG WHO grade II, H3.3K27M	Panobinostat Mebendazole	(1) Temozolomide combined with PARP inhibitor (2) Nivolumab Bevacizumab	Erlotinib	6	12.4	23.0	8.4	9.1	6.3	54 (27)	36 (12)
9	7, F	reRT + nivo	Diffuse astro WHO grade II, H3.3K27M	(1) Panobinostat (2) Newcastle virus combined with dendritic cell infusion and hyperthermia (3) CED valproic acid	Nivolumab Bevacizumab	(1) CED carboplatin (2) Nivolumab Bevacizumab	2.5	12.0	22.9	8.8	11.6	6.9	54 (30)	24 (12)
10	8, F	reRT + nivo	Diffuse midline glioma WHO grade IV, H3K27M	Newcastle virus combined with dendritic cell infusion and hyperthermia	Nivolumab	None	1.5	6.6	17.8	8.8	5.9	2.7	54 (30)	36 (12)
11	11, M	reRT + nivo	DIPG WHO grade IV, H3K27M WT	Temozolomide combined with PARP inhibitor	Everolimus Bevacizumab Nivolumab	None	3.5	9.8	15.9	3.8	4.2	3.0	54 (30)	24 (12)
12	12, M	reRT + nivo	None	None	Nivolumab	***	2.5	11.2	Alive	Alive	10.1	11.6	54 (30)	24 (12)

therapeutics (e.g. temozolamide, capecitabine, bevacizumab, lomustine; Table 1) before or after first recurrence of DIPG. Although there was a significant difference in total number of systemic agents received across groups (median: 4—nivolumab + reRT vs. 3.5—reRT vs. 2—RT; $p = 0.01$), there was no difference between the nivolumab + reRT and reRT groups ($p = 0.71$). The difference in therapies pursued tended to occur after reRT (median 0—nivolumab + reRT vs. 1—reRT vs. 0—RT; $p < 0.001$; Table 2); however, these were small differences overall.

All patients undergoing reRT with or without nivolumab experienced symptom improvement, and several patients regained function important to quality of life, such as ambulation and swallowing. Six patients from the nivolumab + reRT cohort were on dexamethasone (range 2–12 mg daily) at start of reRT and all were able to taper steroids at end of reRT. On follow-up MRI

Table 1 (continued)

13	6, M	RT	None	Vorinostat	None	-	-	-	9.5	-	4	-	54 (30)	-
14	7, F	RT	AA WHO grade III, H3.3K27M	None	Panobinostat	-	-	-	7.4	-	2.2	-	54 (27)	-
15	3, F	RT	Glioblastoma WHO grade IV	Capecitabine	None	-	-	-	3.5	-	0.7	-	55.8 (31)	
16	2, F	RT	None	Bevacizumab Temozolomide Irinotecan	None	-	-	-	5.9	-	NA	-	NA	-
17	8, M	RT	AA WHO grade III, H3K27M	Bevacizumab	None	-	-	-	12.6	-	6.0	-	59.4 (33)	-
18	3, F	RT	None	None	None	-	-	-	15.0	-	NA	-	60 (30)	-
19	12, M	RT	AA WHO grade III, H3.3K27M	None	None	-	-	-	7.1	-	4.4	-	54 (30)	-
20	4, F	RT	None	Motaxefin gadolinium	(1) Cediranib (2) Temozolomide	-	-	-	10.4	-	3.5	-	54 (30)	-
21	7, F	RT	None	Capecitabine	None	-	-	-	5.4	-	1.0	-	NA	-
22	6, F	RT	None	Bevacizumab	(1) Bevacizumab (2) Irinotecan	-	-	-	14.9	-	6.3	-	55.8 (31)	-
23	5, F	RT	Astro WHO grade II	Capecitabine	Sunitinib	-	-	-	6.3	-	2.9	-	NA	-
24	6, F	RT	None	Tipifarnib	None	-	-	-	7.3	-	4.0	-	NA	-
25	9, F	RT	Malignant glioma	Capecitabine	(1) Panitumumab (2) Sunitinib	-	-	-	11.9	-	3.2	-	55.8 (31)	-
26	10, F	RT	Astro WHO grade II	Motexafin-gadolinium	Sunitinib	-	-	-	11.0	-	3.9	-	55.8 (31)	-
27	8, F	RT	None	Gefitinib	None	-	-	-	12.4	-	6.4	-	55.8 (31)	-
28	9, M	RT	None	Gefitinib	(1) Temozolomide (2) Etoposide	-	-	-	9.1	-	4.8	-	55.8 (31)	-
29	11, M	RT	AA WHO grade III Glioblastoma WHO grade IV	(1) Tipifarnib (2) Lenalidomide	Temozolomide	-	-	-	NA	-	2.6	-	55.8 (31)	-
30	13, M	RT	None	Tipifarnib	Cediranib	-	-	-	6.4	-	0.5	-	NA	-
31	12, F	RT	None	Tipifarnib	(1) Lapatinib (2) Temozolomide	-	-	-	7.2	-	4.6	-	NA	-

Radiation treatment categories include *reRT* reirradiation alone, *reRT + nivo* reirradiation with concomitant and adjuvant nivolumab, *RT* no reRT. Pathology diagnosis provided, if available (H3.3K27M = H3.3K27M mutated for patients that underwent biopsy and if H3 K27M status is not listed, no H3 K27M testing was completed). First line treatment equates to therapy offered at initial diagnosis. Treatment at progression is delineated by pre-reRT or post-reRT and were not given concomitantly with nivolumab. Numbers in parentheses indicate sequential treatments. If drugs not delineated by numbers in parentheses, treatment was combination therapy. Patient 12 pursued investigational therapy at an OSH after reRT, treatment records were unavailable

4–6 weeks after completion of reRT, three out of four patients in the reRT group demonstrated radiographic evidence of tumor regression. Four out of eight patients in the nivolumab + reRT cohort exhibited radiographic regression, while three demonstrated increased enhancement likely due to treatment effects, and one did not have available follow up imaging. No patient developed intolerable acute or late toxicity attributable to reRT with or without concomitant nivolumab. One patient receiving ongoing continued monotherapy with nivolumab after reRT developed hyponatremia after the first cycle of nivolumab (CTCAE 4.0 Grade 4). Hyponatremia is a known adverse effect of nivolumab and resolved in this patient withholding of drug [34, 35]. The patient was able to complete

Table 2 Summary statistics for reRT alone, nivolumab with reRT, and upfront RT alone

	reRT (n = 4)	Nivo + reRT (n = 8)	RT (n = 19)	p value
Male, n (%)	0 (0)	4 (50)	6 (32)	0.22
Biopsy, n (%)	2 (50)	7 (88)	8 (42)	0.09
Age at diagnosis, median (years)	5.5	8	7	0.83
Total systemic agents, median (range)	3.5 (3–6)	4 (1–6)	2 (0–3)	**0.01**
Pre-reRT	3 (2–3)	2.5 (0–4)	2 (0–3)	0.19
Post reRT	1 (0–3)	0 (0–3)	0	**< 0.001**
# of Nivolumab Cycles, median (range)	–	3.3 (1–6)	–	–
Time to reRT, median (95% CI, mo)	12.1 (9.4, 13.3)	11.6 (7.5, 21.6)	–	0.90
OS from diagnosis, median (95% CI, mo)	20.4 (14.3, 26.1)	22.9 (16.1, 31.9)	8.3 (6.6, 11.6)	0.44
	20.8 (entire reRT cohort) (16.3, 26.8)			**< 0.0001**
OS from reRT, median (95% CI, mo)	6.0 (2.8, 10.5)	6.8 (4.5, 8.8)	–	0.90
PFS from RT, median (95% CI, mo)	7.7 (4.2, 9.3)	9.6 (5.3, 18.2)	3.9 (2.6, 4.6)	**< 0.0001**
PFS from reRT, median (95% CI, mo)	4.1 (0.5, 8.2)	4.2 (2.7, 8.4)	–	0.90

Total number of systemic agents does not include nivolumab. Statistically significant values in bold, p value < 0.05

five additional cycles of nivolumab without recurrence of hyponatremia.

As compared to the RT cohort, the reRT cohort (with or without nivolumab) exhibited statistically significantly longer median OS (95% confidence interval), 20.8 (16.3, 26.8) months compared to 8.3 (6.6, 11.6) months ($p < 0.0001$; Table 2; Fig. 2). Patients in the RT cohort exhibited disease progression sooner after upfront RT compared to the reRT cohorts (3.9 [2.6, 4.6] mo RT vs. 7.7 [4.2, 9.3] mo reRT vs. 9.6 [5.3, 18.2] mo nivolumab + reRT; $p < 0.0001$; Table 2).

Among patients who received reRT, median OS from diagnosis was slightly longer in the group receiving nivolumab combined with reRT as compared to reRT alone, though not nearing statistical significance (22.9 [16.1, 31.9] mo vs. and 20.4 [14.3, 26.1] mo; $p = 0.44$). The median OS from time of reRT was longer in those receiving nivolumab combined with reRT, also not nearing statistical significance (OS 6.8 [4.5, 8.8] mo vs. 6.0 [2.8, 10.5] mo; $p = 0.90$). The PFS after time of reRT was similar between those receiving nivolumab with reRT and those receiving reRT alone (4.2 [2.7, 8.4] mo vs. 4.1 [0.5, 8.2]; $p = 0.90$; Table 2; Fig. 3). One patient in the nivolumab + reRT cohort (patient #12) remains alive but exhibited disease progression 11.6 months following reRT. This patient had received 2.5 cycles of nivolumab before pursuing experimental chemotherapy at an outside institution (records unavailable, Table 1).

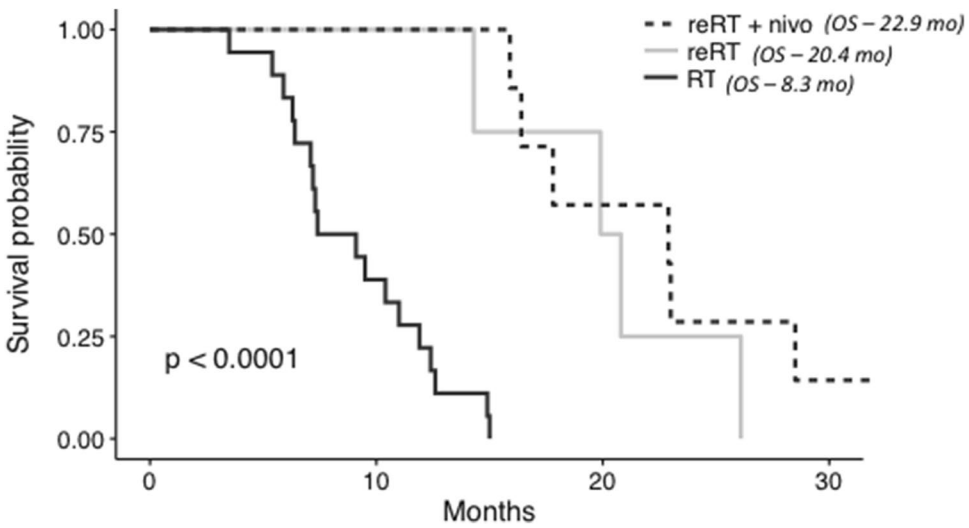

Fig. 2 Kaplan–Meier survival curves for overall survival from time of diagnosis across reRT with nivolumab, reRT alone, and upfront RT alone cohorts (median OS in parentheses of diagram key). P-value derived from log rank test across cohorts

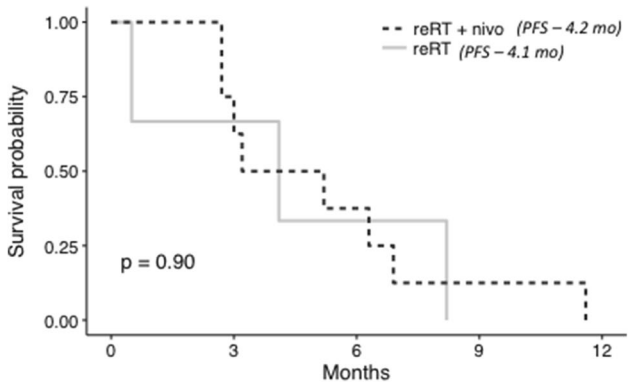

Fig. 3 Kaplan–Meier survival curves for progression-free survival from time of reRT across reRT with nivolumab and reRT alone cohorts (median PFS in parentheses of diagram key). P value derived from log rank test across cohorts

Discussion

DIPG is an extremely aggressive pediatric malignancy with poorly defined treatment standards beyond fractionated radiation therapy. Reirradiation is now offered at our institution at time of DIPG recurrence and provided the patient is at least 6 months from prior RT. Reirradiation has been shown to offer both survival advantage and improve quality of life and we aim to offer reRT for these same benefits [16, 17]. In our report, we describe our experience using combination therapy with reRT and nivolumab for the treatment of patients with recurrent DIPG. We highlight the tolerability of this approach in a heavily pre-treated cohort of patients and demonstrate the potential positive impact this approach has on prolonging overall survival.

In this review, we compared outcomes of patients receiving reRT at time of disease progression with or without concomitant PD-1 inhibition with nivolumab, and also compared outcomes to patients receiving only a single course of upfront RT. Patients with DIPG who received reirradiation at time of recurrence demonstrated better OS as compared to those receiving RT only at time of diagnosis. These outcomes are superior to the survival of patients with DIPG described in a meta-analysis of 29 studies comparing various treatment approaches (n = 973; OS 10.1 mo) and consistent with prior studies illustrating a median OS of 12–19 months after reRT in patients with recurrent DIPG [16, 36–39].

There is slight survival bias in our reRT cohort, since 3 patients in the RT cohort progressed sooner than 6 months after initial RT, which is the threshold that our institution uses as eligibility criteria for reRT. We attribute this finding to potential bias in diagnosis of radiographic progression in the early RT cohort, as compared to diagnoses in more recent years. Whether these patients who had early progression of disease had more aggressive tumors due to differences in tumor biology is unclear since only 3 out of 19 patients in the RT cohort underwent molecular testing. Differences in the rates of biopsy and molecular testing reflect evolving practice patterns at our institution, with patients diagnosed later in chronological time being offered biopsy more frequently. We do recognize that patient #12 appears to be an outlier in our cohort. This patient did not receive a biopsy at presentation due to hemorrhage at diagnosis; however, we suspect the patient's DIPG may have harbored a H3.1 K27M mutation. Patients with these mutations have been described previously as having longer survival than patients demonstrating the more common H3.3 K27M mutation. This may have contributed to the patient's long survival [40, 41]. Nonetheless, in our reRT subgroup, each patient undergoing reRT experienced improvement in clinical symptoms. Also, all patients on dexamethasone in the nivolumab + reRT cohort were able to taper steroids at end of reRT. These results support the use of reRT in the setting of recurrent DIPG, not only for improving OS, but also quality of life through symptom relief.

While our study did not demonstrate a statistically significant survival benefit with the use of combination therapy with nivolumab and reRT, as compared to reRT alone, our findings demonstrate the feasibility and tolerability of this approach for treatment of recurrent DIPG and demonstrated a possible trend towards prolonged OS. Reirradiation in DIPG could result in an increased risk of radiation necrosis (RN), particularly in the setting of hypofractionated radiation and in cases where higher cumulative doses are used and larger field sizes are treated [42, 43]. These additional risks may be increased with the concurrent use of PD-1 inhibition, primarily due to the potentiation of the local immune response [25]. However, in our experience, no patients with recurrent DIPG exhibited severe toxicities following combined treatment with nivolumab and reRT. Consistent with this observation, pseudoprogression did not appear to be prevalent in our cohort, as all patients were determined to ultimately exhibit true progression after reRT. We do acknowledge the inherent difficulties in assessing radiographic progression in the setting of radiation necrosis, use of targeted therapies, and steroids [44–46]. Therefore, progression was frequently determined based on the consensus of a multidisciplinary tumor board and not necessarily based on measurement of tumor volume *per se*. When symptoms did occur, they were typically mild, transient exacerbations of underlying symptoms related to their DIPG or toxicities related to another organ system. We do recognize the challenges with attributing toxicity in such a heavily pretreated population with recurrent DIPG and given the rapid progression that can be seen after salvage interventions. Not included in this cohort is a patient with secondary DIPG after radiation for medulloblastoma ten years prior, who was treated

with nivolumab combined with reRT. This patient was excluded from our analysis due to the expectation that secondary DIPG is intrinsically different than recurrent DIPG. This patient experienced transient worsening of baseline ataxia, dysarthria, and dysphagia after dose 1 of nivolumab. However, symptoms returned to baseline with a 7-day course of oral dexamethasone and the patient continued on nivolumab without therapy delays.

Our experience demonstrated that PD-1 inhibition with nivolumab and reRT for the treatment of patients with heavily pretreated DIPG is well tolerated. The patients in our cohort had undergone several rounds of systemic based agents, and still tolerated reRT combined with nivolumab. The safety profile of radiation therapy with concomitant PD-1 inhibition has previously proven tolerable in newly diagnosed DIPG, as demonstrated by Fried et al. who described only minor adverse events in a cohort of nine patients treated with combination PD-1 inhibition and RT (e.g. nausea, mild to moderate fatigue, mild neutropenia) [30]. This same study reported median overall survival of 15.6 months following DIPG diagnosis, which is superior to previously described outcomes combining RT and chemotherapy [7]. Our study adds to the evidence regarding newly diagnosed DIPG by offering data on combined reRT and PD-1 inhibition in the recurrent setting.

The limitations of our study arise from the small cohort size, the retrospective nature of the study, and the lack of uniformity of therapy approaches in these patients. Overall, only 4 patients in our cohort received reRT alone and only 8 received nivolumab combined with reRT. However, given the rarity of this disease and paucity of published data on therapy responses in the recurrent setting, our results add to the knowledge on the tolerability of PD-1 inhibition given concomitantly with reRT in a population of children where novel therapeutic approaches are desperately needed. Additionally, this report might serve as the basis to support future studies utilizing PD-1 inhibition concomitantly with radiation for DIPG in the upfront setting. We recognize the challenges with identifying progression in the setting of immunotherapy, the potential for later therapeutic benefit even with signs of radiographic progression, and the lack of validated immunotherapy-based assessment criteria for pediatrics [47]. However, by correlating imaging findings with the patient's clinical picture as a whole and through retrospective review of patients' clinical courses, we believe that true progression was accurately determined.

Overall, our current study supports anticipated safety of PD-1 inhibition combined with re-irradiation for the treatment of pediatric DIPG. Future steps will include application of this treatment approach in a clinical trial setting to confirm tolerability and to more fully elucidate potential clinical benefits for this population.

Funding C.N.K. is supported by Frank A. Campini Foundation, Cannonball Kids' Cancer [A129749], and National Institutes of Health National Center for Advancing Translational Sciences [KL2TR001870-This content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH]. The research was supported in part by the William M. Wood Foundation (D.H.K).

Compliance with ethical standards

Conflict of interest The authors of this manuscript have no conflicts of interest and no financial or other interest to disclose.

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