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ORIGINAL ARTICLE

Single institution experience in re-irradiation of biopsy-proven diffuse intrinsic pontine gliomas

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Abstract

Objectives Diffuse intrinsic pontine glioma (DIPG) is the leading cause of death from CNS tumors in children. Multiple clinical trials have failed to show any benefit from systemic therapy in DIPG, and radiation therapy (RT) alone remains the standard of care. Re-irradiation (rRT) for symptomatic relief is an option at disease progression. However, published data on treatment details and outcomes are limited. The objective of this study was to review and report our institutional experience with re-irradiation of patients with biopsy-proven DIPG.

Methods We identified a cohort of pediatric patients with biopsy-proven DIPG with clinical disease progression after initial radiotherapy who received a second course of radiotherapy at our institution. We reviewed patient and treatment characteristics and outcomes.

Results Between January 2014 and July 2018, we identified five patients with progressive DIPG who received re-irradiation. Re-irradiation was well tolerated with no serious adverse events reported and all patients experiencing stable to improved neurologic function during treatment. Median survival from completion of re-irradiation was 116 days (range 62 to 159 days). Median overall survival from time of diagnosis was 16.3 months (range 13.0 to 18.0 months), which is longer than the historical average of less than 12 months. In patients with available postmortem neuropathology, common findings were Wallerian degeneration and necrosis.

Conclusions In our experience, re-irradiation is safe and feasible for patients with DIPG with symptomatic disease progression following initial radiotherapy treatment.

Keywords Diffuse intrinsic pontine glioma · DIPG · Re-irradiation · Children

Introduction

Diffuse intrinsic pontine glioma (DIPG) is a highly aggressive pediatric brain tumor. With a 5-year survival rate of less than 3%, DIPG is also the leading cause of death among pediatric CNS cancers [1]. Arising from the structures of pons, these tumors are not amenable to surgery. Radiotherapy alone remains the standard of care as the only treatment modality with sufficient evidence to suggest it can alter the clinical course of the disease [2]. However, the role of radiotherapy in this disease is still ultimately palliative despite multiple clinical trials investigating dose escalation, altered fractionation, and radiosensitizing agents [3–9]. Due to the aggressive nature of this disease, CNS progression after initial RT is common and re-irradiation has been shown to be safe and effective in providing additional palliation [10, 11].

Owing to difficulty obtaining a tissue biopsy of the brainstem, diagnosis of DIPG has to this point been largely based on clinical and radiographic findings. However, with advances in neurosurgical techniques and a need for greater study of the biological basis of the disease, stereotactic brainstem biopsies are becoming more common [12]. While previous case series in re-irradiation of DIPG in the literature have relied on radiographic diagnosis, in this paper we provide treatment details and outcomes data after re-irradiation for five patients with biopsy-proven DIPG.

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Methods

We identified a cohort of all pediatric patients with DIPG treated with re-irradiation at our institution between 2015 and 2018 for a total of five patients. All five patients were biopsied at the time of diagnosis. Pathologic confirmation was based on pre-WHO 2016 histologic appearance of infiltrating gliomas as H3-K27M testing was not routinely performed at our institution at the time of biopsy for this patient cohort. We reviewed patient characteristics, treatment details, postmortem pathology, and laboratory results to identify any possible correlates with clinical outcomes.

Results

We identified five patients with progressive DIPG who received re-irradiation between January 2014 and July 2018 (Table 1). All patients were treated in our department with intensity modulated 6 MV photons delivered with a helical tomotherapy unit. Disease progression was documented radiographically in all cases prior to re-irradiation (Fig. 1). All patients had progressive neurologic symptoms at the time of documented radiographic progression. The median time from initial treatment to re-irradiation was 10 months, with a range between 8.4 and 12 months. Three of the five patients received systemic chemotherapy concurrent with re-irradiation (erlotinib plus bevacizumab). All patients with the exception of one (aged 10 years at time of diagnosis) were treated under anesthesia. Re-irradiation was well tolerated in all patients with no serious treatment-related toxicity reported. Improved neurologic function was reported in four of the five patients during re-irradiation. One patient saw stable neurologic function without overt improvement during re-irradiation. All patients received corticosteroids concurrent with re-irradiation.

Mean initial RT dose was 55 Gy delivered in 1.8 Gy daily fractions (range 50.4 to 59.4 Gy). Re-irradiation doses ranged between 20 and 24 Gy in 2.0 Gy daily fractions. Median survival from time from re-irradiation was 116 days (range 62 to 159 days). Mean and median survival from time of initial diagnosis were 15.6 months and 16.3 months, respectively (range 13.0 to 18.0 months). Serum LDH levels increased in all patients during the course of re-irradiation (Table 1). Cumulative radiation dose, reported as equivalent dose in 2.0 Gy fractions or EQD2 (a way to correct for the biological impact of different fraction sizes), did not appear to correlate with survival (Table 1). In patients with available postmortem neuropathology (three of five patients), common findings were treatment-induced Wallerian degeneration and focal necrosis within the pontine tumor volume without overt necrosis involving normal structures (Table 1). All patients with available postmortem neuropathology demonstrated extensive progressive DIPG.

Table 1 Patient and treatment characteristics. yrs, years; Gy, Gray; fx, fractions; mos, months; EQD2, equivalent dose in 2 Gray fractions; α/β, alpha/beta ratio; LDH, lactate dehydrogenase; u/L, units/liter

Patient	Age (yrs)	Dose RT (1.8 Gy/fx)	Dose rRT (2.0 Gy/fx)	Time to rRT (mos)	Cumulative EQD2 (Gy) α/β = 2	Cumulative EQD2 (Gy) α/β = 10	Survival from last RT (days)	Overall survival (mos)	Concurrent chemo	Postmortem pathology	LDH rRT start (u/L)	LDH rRT end (u/L)	ΔLDH (+%)
1	10	59.4	24	12.0	80.4	82.4	79	16	Y	Focal necrosis, Wallerian degeneration	677	953	40.8
2	3	57.6	24	8.4	78.7	80.6	78	12.8	Y	Diffuse necrosis, Wallerian degeneration	367	513	39.8
3	4	50.4	20	10.4	67.9	69.6	120	16.5	N	N/A	478	588	23
4	5	59.4	24	11.0	80.4	82.4	116	13.9	Y	Focal necrosis, Wallerian degeneration	341	430	26.1
5	3	50.4	24	12.0	71.9	73.6	160	17.8	N	N/A	243	273	12.3

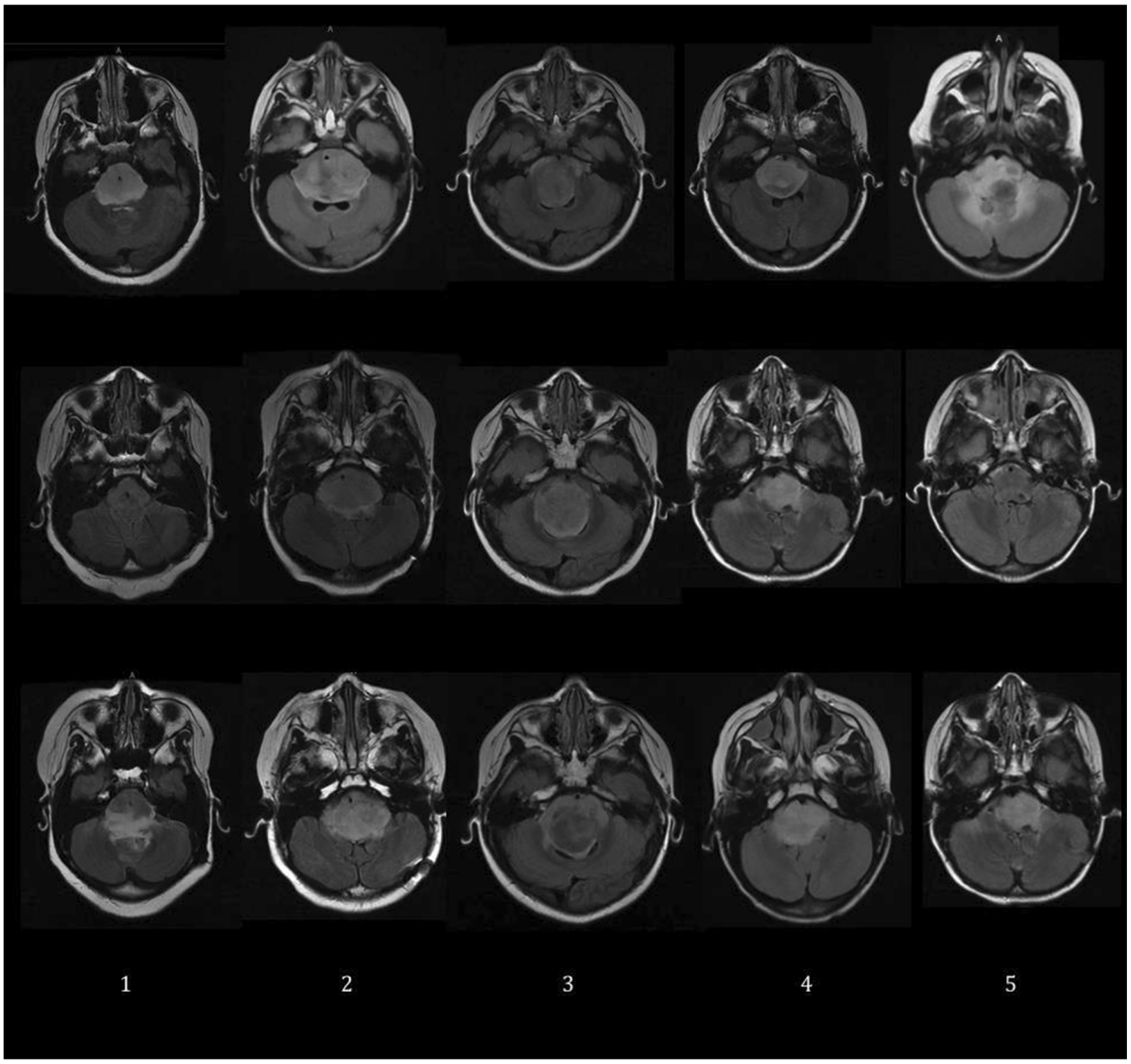

Fig. 1 T2 FLAIR sequence MRI studies captured prior to first treatment (top row), after first radiation treatment completion (middle row), and prior to re-irradiation (bottom row) for each patient one through five

Discussion

Diffuse intrinsic pontine glioma (DIPG) is a pediatric cancer that carries a universally poor prognosis. Symptoms from DIPG, especially neurological symptoms, can severely affect the patient's quality of life. Radiation therapy has been the mainstay of therapy used to treat these children as the only modality shown to prolong survival while providing meaningful palliation of symptoms.

Outside of therapeutic radiation, limited options exist for the treatment of DIPG. Studies evaluating the addition of the chemotherapeutic agent temozolomide to radiation therapy have failed to show a significant improvement in overall survival [7–9]. In fact, to date, no systemic therapy regimen has been shown to improve survival in DIPG. As such, efforts have been made to further optimize radiation regimens for this disease. Multiple studies have compared hypofractionated radiation therapy to conventionally fractionated radiation therapy with no significant improvement in survival [3–6]. To date conventionally fractionated radiation (1.8 to 2 Gy per fraction) therefore remains the standard of care for this disease. However, many patients with DIPG will show symptoms of CNS progression months following initial irradiation and may benefit from a second course of radiation therapy.

Radiation alone remains the sole treatment modality proven to alter the clinical course of DIPG, and there is mounting evidence in the literature supporting the use of re-irradiation in select patients. Lassaletta et al. retrospectively reviewed data of patients with DIPG treated with re-irradiation at Canadian centers. Re-irradiation was given focally in fourteen patients with doses ranging from 21.6 Gy to 36 Gy with conventional fractionation. All but three patients showed neurological improvement [10]. When compared to a historic cohort of forty-six consecutive patients, the median time from progression to death was 92 days in the non-irradiated group versus 218 days in the re-irradiated group. The re-irradiated group also had a

median overall survival from time of diagnosis of 19.6 months, which is significantly longer than historical controls and is also longer than the median overall survival for our cohort of patients by several months.

It is worth noting again that our study included only patients with biopsy findings consistent with DIPG. Additionally, our cohort included only African American and Hispanic patients—demographics consistently shown to have poorer outcomes in childhood cancer [13]. Despite these possible adverse prognostic features, the median survival from time of diagnosis in our cohort was 16.3 months, which is higher than the 10–11 months typically cited in the literature for patients largely treated without re-irradiation [1, 14]. This finding is consistent with several other retrospective studies demonstrating effective palliation and a trend towards improved survival with re-irradiation. In a more recent example, Janssens et al. published a matched-cohort analysis of 85 patients with DIPG treated at multiple European centers with and without re-irradiation, with a finding of significantly improved median survival at 13.7 months for patients treated with re-irradiation versus 10.4 months for those not treated with a second course [15]. Consistent with other retrospectives studies, our patient cohort also demonstrated stable to improved neurological function during re-irradiation with no serious treatment-related adverse events reported.

Four of the five patients in our cohort were treated with re-irradiation to 24 Gy with conventional fractionation, a regimen shown to be safe and effective in a phase 1/2 study of dose escalation in DIPG re-irradiation [16]. However, unlike in the dose escalation study, most of our patients received concurrent chemotherapy and all three of the patients for whom postmortem pathology was available demonstrated some degree of focal pontine necrosis. Whether this is attributable to the concurrent use of chemotherapy is uncertain. However, given the already controversial role of chemotherapy in the management of DIPG, it may be prudent to avoid concurrent administration at the time of re-irradiation until additional data are available to support this practice.

The observation of rising serum LDH during the course of re-irradiation in our patients is purely a hypothesis-generating observation. There are data in adult cancer patients with brain metastases to suggest that serum LDH is a potentially useful prognosticator [17]. In one retrospective study of small cell lung cancer patients with brain metastases undergoing treatment with whole-brain radiation, after controlling for confounding clinical factors such as performance status, patients with serum LDH in the normal range had significantly higher median survival than patient with elevated serum LDH [18]. It is possible that monitoring serum LDH kinetics in DIPG patients may aid in clinical decision-making particularly when it comes to re-irradiation; however, more research in the area is clearly needed. It is also worth noting that the three patients who received systemic therapy concurrent with re-irradiation had relatively higher increases in serum LDH compared to the patients not receiving systemic therapy.

In summary, our experience based on our small patient cohort is that re-irradiation is safe and feasible for patients with DIPG with symptomatic disease progression following initial radiotherapy treatment. This adds to a growing body of evidence on the safety and efficacy of re-irradiation. Re-irradiation should continue to be offered in select patients with symptomatic progression after initial treatment.

Declarations

Conflict of interest On behalf of all authors, the corresponding author states that there is no conflict of interest.

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