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ORIGINAL PAPER

Pediatric diffuse intrinsic pontine glioma patients from a single center

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Abstract
Background The prognosis of children with diffuse intrinsic pontine gliomas (DIPG) is dismal. This study aims to evaluate the characteristics and treatment outcome of children with DIPG in a single center.
Methods We reviewed the outcome of children with DIPG treated at the Oncology Institute of Istanbul University from February 1999 to May 2012.
Results Fifty children (26 female, 24 male) with the median age of 7 years were analyzed. The median duration of symptoms was 30 days. All patients received radiotherapy (RT). Before the year 2000, 12 patients received only RT. Thirty-eight had concomitant and/or adjuvant chemotherapy with RT. Between 2000 and 2004, 17 patients received *cis*-platinum or vincristine as sensitizers during RT and CCNU + vincristine combination after RT. Since 2004, 21 patients received temozolomide (TMZ) concomitantly during RT and as adjuvant chemotherapy after RT. The median survival time of all patients was 13 months (1–160 months). Patients receiving RT + TMZ had a significantly higher overall survival than patients with only RT (p=0.018). Patients receiving RT + chemotherapy other than TMZ also had a significantly higher overall survival than patients receiving only RT (p=0.013). Patients receiving RT + TMZ + and chemotherapy other than TMZ had a significantly higher survival than patients receiving only RT (p=0.005).
Conclusion In our series, patients receiving RT + TMZ and also patients receiving RT + chemotherapy other than TMZ had a significantly higher overall survival than patients treated with only RT. Hence, administering chemotherapy during and after RT seems to prolong survival in some DIPG patients.

Keywords Diffuse pontine glioma · Pediatric · Radiotherapy · Temozolomide

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Introduction

Brain stem tumors are one of the most malignant pediatric brain tumors [13, 22]. They account for 12.2 % of all pediatric brain tumors [22, 29]. Among all brain stem tumors, 80 % are diffuse intrinsic pontine gliomas (DIPG) [10, 19, 20]. Typical magnetic resonance imaging (MRI) findings and the impossibility to completely resect most tumors lead these patients to be treated without histological confirmation [2, 8]. Radiotherapy (RT) is known to extend survival and frequently improve the quality of life for a period of time [8]. A positive role of chemotherapy has been suggested in some retrospective analysis [28], but the effect appears to be small. After radiochemotherapy, these tumors shrink but recur rapidly. Survival outcome for this group of tumors are worse than any other CNS tumor. Median time until progression is 5–6 months, median survival time is usually less than 1 year, and survival beyond 2 years from diagnosis is less than 10 % [12, 14]. There seems to be no progress in the last 20 years [3–7, 9–11, 14–18, 21, 22, 26]. In this retrospective study, we documented the outcome and

survival analysis of DIPG patients who received RT only and those who received RT and concomitant chemotherapy.

Materials and methods

We retrospectively reviewed a total of 50 DIPG patients treated at the Oncology Institute of Istanbul University from February 1999 to May 2012. During this period, a total of 512 pediatric patients with brain tumors were admitted. Patients presented with clinical features emerging from cranial nerve deficits, motor nerve disability, cerebellar dysfunction, and MRI evidence of a large, expansile lesion with irregular margins. The diagnosis of DIPG was clinically made after evaluation by a pediatric oncologist, radiation oncologist, neurosurgeon, and radiologist in the multidisciplinary tumor board. All patients had adequate hematologic, renal, and hepatic functions (hemoglobin level>11 g/dl, total leukocyte count>4,000/mm^3 with absolute neutrophil count>1,500/mm^3 and platelet count>100,000/mm^3; liver enzyme level<2.5 upper limit of normal; and serum creatinine level<1.5 upper limit of normal). Cranial MRI was obtained from all patients at diagnosis and was repeated every 3 months during treatment and after therapy. All patients received RT as the standard treatment. In our institution, RT treatment was given solely without concomitant/adjuvant chemotherapy before the year 2000 (group 1 RT only). RT was administered to the tumor bed plus 2-cm margins with a conventional fractionation of 180–200 cGy once a day for 5 days a week within 6 weeks, with a total dose of 54 Gy. As fractionated daily RT dose was diminished in patients under 3 years of age, four patients were given 60 Gy hyperfractionated RT, a biologically equivalent dose of 54 Gy. The treatment protocol changed after 2000 by the addition of chemotherapy as concomitant/adjuvant treatment after RT. From 2000 to 2004, *cis*-platinum 40 mg/m^2/week or vincristine 1.5 mg/m^2/week were used as sensitizers concomitantly during RT, and the combination of CCNU 100 mg /m^2 every 4 weeks and vincristine 1.5 mg/m^2 every 4 weeks was used after RT (group 3, RT and other chemotherapy). Since 2004, temozolomide (TMZ) (75 mg/m^2/day p.o.) for 6 weeks was used concomitantly during RT, followed by TMZ (200 mg/m^2/day p.o.) for 5 days with a 28-day cycle after RT as adjuvant chemotherapy for 12 cycles (group 2, RT and TMZ). TMZ was suspended for an absolute neutrophil count lower than 1,500/mm^3 and platelet count lower than 100.000/mm^3.

Statistical analysis

The median survival was evaluated in the whole group: in group 1, RT only; in group 2, RT and TMZ; and in group 3, RT and other chemotherapy, and the comparison was made between groups 1 vs. 2, group 1 vs. 3, and group 1 vs. any chemotherapy (groups 2 and 3 combined). Overall survival was assessed by the Kaplan–Meier method in all groups, and survival between groups was compared by the logrank test.

Results

The median age of 50 patients (26 female and 24 male) was 7 years (6 months–16 years). They presented with a median period of 30 days (2–630 days) of symptom duration and history. No patient in this series had neurofibromatosis type 1. The most frequent clinical finding was ataxia in 32 (64 %) patients, followed by strabismus in 31 (62 %) patients, and motor weakness in 22 (44 %) patients. The most frequent cranial nerve involvement was the sixth cranial nerve. All patients received RT as the standard treatment. Before the year 2000, 12 patients received RT only (group 1, RT only). From 2000 to 2004, 17 patients received *cis*-platinum or vincristine as sensitizers during RT, and CCNU + vincristine combination after RT (group 3, RT and other chemotherapy). After the year 2004, 21 patients received TMZ concurrently with RT and after RT (group 2, RT and TMZ). Three of the patients in this group were biopsied, and the results were pilocytic astrocytoma. During TMZ treatment, clinical deterioration was thought to be due to pseudoprogression in three patients, and TMZ was not stopped. The patients recovered after dexamethasone treatment which was gradually stopped. Twelve total cycles were planned in 21 patients. After 8 cycles of TMZ, the dose was diminished to 75 % in ten patients, but the intervals had to be prolonged in the last 2 cycles to a 42-day cycle in three patients due to thrombocytopenia. Forty thrombocyte transfusions were given as the platelet count< 20,000/mm^3. No patients required erythrocyte transfusions. There was no hospitalization due to febrile neutropenia. The median survival time among all patients was 13 months (1–160 months) (Table 1). Group 2 patients who received RT and TMZ had a significantly higher overall survival than patients in group 1 who only received RT (p=0.018). Group 3 patients who received RT and other chemotherapy had a significantly higher survival than patients in group 1 who only received RT (p=0.013). Patients receiving any chemotherapy (groups 2 and 3 combined) had a significantly higher survival than patients in group 1 who only received RT (p=0.005) (Fig. 1; Table 1). At 1-year follow-up, there were no survivors in group 1 who only received RT; 13 of 21 patients in group 2 who received RT and TMZ were dead of disease; 13 of 17 patients in group 3 who received RT and other chemotherapy were dead of disease; thus, 26 of 38 patients are failures in groups 2 and 3 combined (Table 1). In group 2, ten patients who received RT and TMZ survived at 2 years, and five patients survived at 3 years; three patients in group 3 who

Table 1 Comparison of median survival and 1-year survival between group 1, group 2, group 3, and group 2 + 3

Group	Event[a]/case	Median survival (months)	1-Year survival rate	Logrank (%)	*p*
Group 1	12/12	12 (3–20)	41.7±14.2		
Group 2	13/21	12 (1–160)	55.3±11.2	5.60	0.018[b]
Group 3	13/17	15 (1–132)	47.5±12.9	6.23	0.013[c]
Group 2 + 3	26/38	15 (1–160)	60.8±8.2	7.810	0.005[d]

[a] Death of the patient

[b] Comparison of group 1 (patients receiving only radiotherapy) and group 2 (patients receiving radiotherapy and temozolomide)

[c] Comparison of group 1 and group 3 (patients receiving radiotherapy and other chemotherapy)

[d] Comparison of group 1 and group 2 + 3 (patients receiving radiotherapy and any chemotherapy)

received RT and other chemotherapy also survived at 3 years. Survival at 2 and 3 years was significantly higher in patients receiving any chemotherapy (groups 2 and 3 combined) vs. group 1 who only received RT (Table 2). Ten patients died on the ventilator; eight died in 5 days. Only two patients who received RT and TMZ survived 2 months upon ventilator in group 2.

Discussion

DIPG are currently associated with a very poor prognosis due to their unresectable nature, devastating neurological lesions associated with the local extension, and poor response to adjuvant therapy. The origin of these tumors is glial in more than 90 % of the cases, with 70 % of the tumors

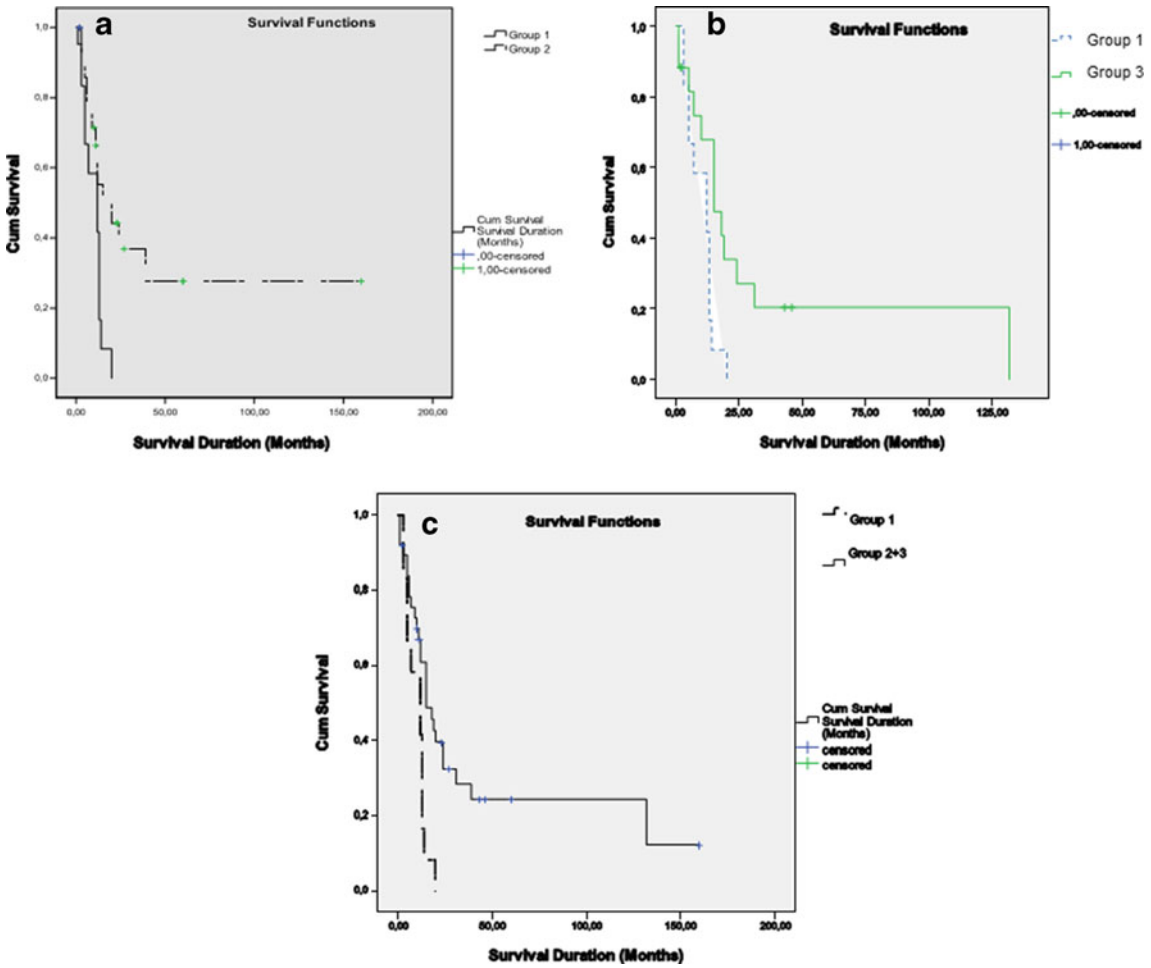

Fig. 1 **a** Comparison of overall survival for group 1 RT only (*solid line*) and group 2 RT and TMZ (*dashed line*). **b** Comparison of overall survival for group 1 RT only (*dashed line*) and group 3 RT and other chemotherapy (*solid line*). **c** Comparison of overall survival for group 1 RT only (*dashed line*) and group 2 + 3 RT and any chemotherapy (*solid line*)

Table 2 Survival rates of patient groups at 1, 2, and 3 years

Group	Number	1 year (%)	2 years (%)	3 years (%)
Group 1	12	42	0	0
Group 2	21	55	37	37
Group 3	17	47	27	20
Group 2 + 3	38	61	32	28

Group 1, patients receiving only radiotherapy; group 2, patients receiving radiotherapy and temozolomide; group 3, patients receiving radiotherapy and other chemotherapy; and group 2 + 3, patients receiving radiotherapy and any chemotherapy

arising in patients younger than 7 years of age (median age at diagnosis, 5–9 years) [19, 22]. Similarly, our study group had a median age of 7 years (6 months–16 years) at diagnosis. Manifestations include combinations of cranial nerve palsies and ataxia. Cranial nerves VI and VII are the most commonly affected, although cranial nerves III, IV, IX, and X may be also compromised [19, 22]. We established similar findings in our study as the most frequent clinical findings were ataxia, strabismus, and motor weakness.

RT is the standard treatment for DIPG with external local field RT at a total dose of 54–60 Gy in 6 weeks. Many techniques such as hyperfractionated RT and increasing RT doses to 78 Gy have been tried with no alteration in time to progression [16, 23]. Several chemotherapeutic agents investigated previously offered no significant improvement. Doz et al. [9] and Bernier-Chastagner et al. [3] used radiosensitizers during RT and reported no improvement in survival. Wagner et al. [28], in the HIT-GBM data reported the 1-year overall survival rate as 45.8 % in patients treated with both RT and CT, although no patients in this database survived longer than 3.9 years. Massimino et al. [21] established no survival advantage within four protocols used in their mono-institutional study in 20 years' time.

After TMZ was reported to be the standard chemotherapy for adults with newly diagnosed glioblastoma, studies of TMZ on children with high-grade gliomas were undertaken. It was also tried in other relapsed brain tumors including DIPG in children [1, 18]. TMZ produces its cytotoxicity by the DNA methylation of the guanine at the O_6 position. It may be useful to evaluate the methylguanine DNA methyltransferase (MGMT) promoter methylation status of the tumor tissue. If there is an expression of MGMT recovery enzyme, it may take away the methyl or alkyl group and put the normal guanine in place and thus cause resistance to TMZ [25]. Despite the initial positive responses observed among children with high-grade gliomas treated in phase I trials, Broniscer et al. [4] reported a disappointing response to TMZ in children. Accordingly, Sirachainan et al. [26], Jalali et al. [15], Kim et al. [17], Chassot et al. [5], and Cohen et al. [7] established no improvement in the outcome of DIPG patients with RT–TMZ (Table 3). Small series have recently suggested that the biology of DIPG is fundamentally different from that of supratentorial anaplastic astrocytoma and glioblastoma multiforme [24, 30]. Another point is that epigenetic silencing of the MGMT gene by promoter methylation is suggested to enhance the cytotoxic impact of TMZ [25]. The limitations of those studies are the lack of information about the biologic character or the MGMT promoter methylation status of the tumor tissues of patients like those in our series. It may be that some tumors may be more responsive to MGMT and have a better response to TMZ. In our series, although there was no survivor at 2 and 3 years among only RT receivers, ten patients survived at 2 years and five patients survived at 3 years in group 2 who received RT and TMZ. Three patients in group 3 who received RT and other chemotherapy also survived at 3 years. Thus, we suggest concurrent and/or adjuvant chemotherapy with RT; it might improve survival in some DIPG patients. Moreover, there might be other prognostic factors like more frequent visits for weekly chemotherapy administration and requirement for blood counts in the last decade according to changes in chemotherapy in our series. Thus, the symptoms and positive findings of disease

Table 3 Summary of the studies reporting the results of concomitant and adjuvant temozolomide in children with diffuse intrinsic pontine glioma

Reference (country)	Year	Nature of the study	TMZ[a] dose	Number	1-Year survival (%)	Median survival (months)
Broniscer et al. [4] (USA)	2005	Prospective	200×6	29	48	12
Cohen et al. [7] (COG)	2011	Prospective	90/200×10	63	40	9
Jalali et al. [15] (India)	2010	Prospective	75/200	20	35	9
Chiang et al. [6] (Taiwan)	2010	Prospective	75/150	18	51	12.3
Sirachainan et al. [26] (Thailand)	2008	Prospective	75/200	12	58	13.5
Kim et al. [17] (Korea)	2010	Prospective	75/200	12	58	12.7
Chassot et al. [5] (France)	2011	Prospective	75/200×6	21	50	11.7
Current study (Turkey)	2012	Retrospective	75/200×12	21	55	12

[a] Temozolomide dose during RT/after RT and number of cycles, month/months

progression could be met earlier, and decision of arranging a shunt or percutaneous endoscopic gastrostomy might have a contribution on survival duration concurrently with the technical improvement of these palliative measures over the study period. In addition to that, the parents are more aware of the behavioral changes of their children, and the governments can enable them more improved social facilities such as home nursing or hospice services in time. Hence, more free time out of bed might possibly enhance the well-being of the children as Temel et al. [27] reported that early palliative care led to significant improvements in both quality of life and mood.

Our retrospective study has the limitation of a long duration so that standardization of chemotherapy and RT applications is not possible, but development in RT technicals might also contribute such improved results in time.

In conclusion, TMZ and/or other chemotherapeutic agents might change the poor outcome of children with newly diagnosed DIPG. The limitation of this study is its retrospective design, long duration, and the small sample size. The complex biology of DIPG renders an unselected single-agent approach less likely to be effective. Instead, a multitargeted approach seems to be required to improve the prognosis.

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Conflict of interest The authors have no conflict of interest to declare.

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