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ORIGINAL PAPER

Diffuse intrinsic pontine glioma in children and adolescents: a single-center experience

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Abstract
Background Patients with diffuse intrinsic pontine glioma (DIPG) have a very poor prognosis. Only radiotherapy (XRT) has proven to be effective in delaying the disease progression. Several chemotherapy schedules have been applied so far, but none demonstrated significant improvements in progression and survival.
Methods We retrospectively analyzed the clinical data of children diagnosed with DIPG at our center (Pediatric Hospital "Regina Margherita," Turin, Italy) between 1999 and 2013. Progression-free survival (PFS) and overall survival (OS) were used to describe the outcomes.
Results Twenty-four children were included in our report. Patients diagnosed before March 2003 (n=12) were treated with XRT and vincristine (VCR); the remaining 12 patients received XRT and temozolomide (TMZ). Progression-free survival was 18.8 % at 1 year (SE=7.6 %), while overall survival was 44.1 % at 1 year (SE=9.9 %). Median PFS was 8.1 months, whereas median OS was 11.2 months. No statistically significant difference in PFS or OS was evidenced between the two treatment groups.
Conclusion Radiotherapy followed by VCR or TMZ allows obtaining results that are in line with previous reports, with no advantages over other similar treatment schedules.

DIPGs are challenging tumors with a dismal outcome. Further research and newer therapies are urgently needed in order to achieve improvements in survival.

Keywords Diffuse intrinsic pontine glioma · Brainstem tumor · Vincristine · Temozolomide · Radiotherapy · Pediatric oncology

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Introduction

Diffuse intrinsic pontine glioma (DIPG) is an almost invariably lethal cancer. The 18-month overall survival (OS) is estimated at about 10 % in most series, with a median survival of about 9 months [11, 22].

Radiotherapy has proven to be useful in delaying disease progression, but in most cases, its effects are only transient [9]. Neither hyperfractionation nor higher dosing have shown additional efficacy [3, 16, 18, 20].

Chemotherapy has been employed with different strategies as follows: in radiosensitization, in high-dose schedules with hematopoietic stem cell rescue, or at low doses for prolonged periods, but results are mostly discouraging, with progression-free survival (PFS) and OS remaining almost paired with patients treated only with radiotherapy [15, 18].

Vincristine (VCR) and temozolomide (TMZ) have been widely used in the treatment of children with DIPG, even though they failed to demonstrate clear improvements in the outcome [2, 4, 6, 12, 15].

We report about 24 pediatric patients with DIPG who were treated at our institution from 1999 to 2013. All patients were

irradiated and received either VCR or TMZ as initial therapy. We describe clinical characteristics and treatment in our cohort, trying to compare the outcome of patients treated with VCR with the ones treated with TMZ.

Methods

Patients

We retrospectively reviewed the medical records of 24 children diagnosed with DIPG at "Regina Margherita" Children's Hospital in Turin, Italy, between January 1999 and September 2013.

All patients were initially treated with radiotherapy, along with VCR or TMZ as radiosensitizer. Adjuvant chemotherapy, either VCR or TMZ, was started again 4–6 weeks after the end of radiotherapy.

All patients underwent gadolinium-enhanced MRI at diagnosis, with imaging features consistent with the diagnosis of DIPG. MRI was performed again 4–6 weeks after radiotherapy discontinuation, and then on a 3-month basis, or in case of suspect disease progression. Biopsy was performed only if the neurosurgeons believed that surgery could be of clinical benefit for the patient [1, 5].

Treatment

Radiotherapy was administered in daily single fractions, Monday through Friday, up to a median total dose of 54 Gy (min 48.6 Gy, max 55.8 Gy).

Patients diagnosed before March 2002 (n=12) received weekly intravenous vincristine (1.5 mg/m^2) as a radiosensitizer during radiotherapy, followed by weekly adjuvant therapy with vincristine, starting 4–6 weeks after the end of radiotherapy. The remaining patients (n=12) were treated similarly, but with the use of oral temozolomide at 60 mg/m^2 daily during radiotherapy, and later at 180 mg/m^2 for 5 days every 28 days, starting 4–6 weeks after the end of radiotherapy.

Response evaluation

Response was determined on MRI scans using the largest two-dimensional tumor measurements on T2-weighted and/or FLAIR sequences. Partial remission was defined if there was at least a ≥25 % reduction in the size of the largest pretreatment cross-sectional tumor area; progressive disease, if there was a ≥25 % increase in the tumor size; and stable disease, if there was either increase or reduction of less than 25 % in the tumor size.

Statistics

PFS was defined as time from diagnosis to progression, either clinical or radiological. OS was defined as the duration of survival from diagnosis to death from any cause. Survival curves were built according to Kaplan and Meier's method [13]. Differences between the two treatment groups were assessed using the log-rank test [21].

Results

Patients' clinical features, treatment, responses, and outcome are shown in Table 1.

Median age at diagnosis was 6.1 years (range 2.9–16.6 years). There were 13 females and 11 males.

Biopsy was performed only in two cases: in patient 21, at diagnosis, and in patient 22, after disease progression (in the latter, surgery was performed in another center). In both cases, histology disclosed a high grade glioma. Two patients needed surgery for hydrocephalus at diagnosis (ventriculoperitoneal shunt in patient 2 and ventriculocysternostomy in patient 22).

The median latency time between the first symptoms and diagnosis was 4 weeks (min=2, max=20).

Out of 24 patients, only 1 (4 %) had disease progression immediately after radiotherapy; one had complete remission. Seven patients (29 %) had stable disease. Fifteen patients (63 %) had partial remission. The treatment responses were sustained through maintenance chemotherapy until disease progression.

Progression-free survival was 66.7 % at 6 months (SE=9.3 %), 18.8 % at 1 year (SE=7.6 %), 4.7 % at 18 and 24 months (SE=3.2 %) (Fig. 1). Median PFS was 8.1 months. Overall survival was 87.5 % at 6 months (SE=6.6 %), 44.1 % at 1 year (SE=9.9 %), 22 % at 18 months (SE=8.7 %), and 11 % at 24 months (SE=5.9 %). Median OS was 11.2 months (Fig. 2).

Outcomes were compared between the two groups of treatment (VCR vs. TMZ) by log-rank test, but differences were not statistically significant.

Median PFS was 8.1 months for the VCR group, while it was 7.9 for the TMZ group. Median OS was 11.6 months for the VCR group, while it was 9.7 for the TMZ group.

At 6 months, PFS was 83.3 % for patients treated with VCR (SE=10.7 %), while it was 58.3 % for patients treated with TMZ (SE=13.3 %). At 12 months, PFS was 25 % for patients treated with VCR (SE=10.8 %), while it was 20.8 % for patients treated with TMZ (SE=13.1 %) (Fig. 3).

At 12 months, OS was 50 % for patients treated with VCR (SE=13.3 %), while it was 38.1 % for patients treated with TMZ (SE=14.9 %). Nonetheless, after 18 months, overall survival was lower in patients treated with VCR (16.7 %, SE=10.8 %) than in patients treated with TMZ (28.6 %, SE=13.9 %) (Fig. 4).

Table 1 Patients' characteristics and outcome

Pt	Sex	Age at diagnosis	Symptoms at diagnosis	Surgery	Treatment	Other treatment	XRT dose	Symptoms delay (weeks)	Response after XRT	Progression	PFS	Death	OS
1	M	4.5	Gait, cranial nerves	No	VCR + XRT	–	54	8	PD	Yes	3.0	Yes	10.3
2	M	5.6	Gait, cranial nerves, headache	VPS	VCR + XRT	–	55.2	8	SD	Yes	11.6	Yes	13.6
3	F	3.7	Gait, cranial nerves, vision	No	VCR + XRT	–	55.8	4	PR	Yes	12.2	Yes	25.1
4	M	4.3	Cranial nerves, vision	No	VCR + XRT	–	54	10	SD	Yes	12.8	Yes	23.3
5	F	11.4	Gait, cranial nerves, vision	No	VCR + XRT	–	54	8	PR	Yes	12.8	Yes	17.6
6	M	5.7	Gait	No	VCR + XRT	–	54	8	SD	Yes	8.1	Yes	9.8
7	M	3.9	Gait, cranial nerves	No	VCR + XRT	–	54	6	PR	Yes	7.8	Yes	11.6
8	F	7.0	Gait, vision	No	VCR + XRT	–	54	12	PR	Yes	8.4	Yes	14.3
9	F	4.8	Cranial nerves, vision	No	VCR + XRT	–	55.8	2	PR	Yes	6.1	Yes	9.6
10	F	4.7	Gait, cranial nerves, vision	No	VCR + XRT	–	48.6	4	PR	Yes	3.5	Yes	4.1
11	M	4.2	Gait, cranial nerves	No	VCR + XRT	–	54	2	PR	Yes	8.7	Yes	12.7
12	F	7.4	Gait, vision	No	VCR + XRT	–	54	4	PR	Yes	7.8	Yes	11.0
13	F	12.1	Headache, drowsiness, gait	No	TMZ + XRT	–	54	4	PR	Yes	9.7	Yes	9.7
14	F	6.9	Cranial nerves, headache	No	TMZ + XRT	–	54	4	PR	Yes	18.4	Yes	19.3
15	F	7.6	Gait, cranial nerves	No	TMZ + XRT	–	55.8	15	SD	Yes	3.0	Yes	7.6
16	M	2.9	Gait, cranial nerves, sphynterial dysfunction	No	TMZ + XRT	–	54	2	SD	Yes	4.5	Yes	6.1
17	F	6.5	Cranial nerves	No	TMZ + XRT	–	54	2	PR	Yes	5.4	Yes	8.6
18	M	12.1	Headache	No	TMZ + XRT	oral VP16	50.4	20	CR	Yes	46.7	No	61.2
19	F	11.4	Cranial nerves, hemistenia	No	TMZ + XRT	–	54	4	PR	Yes	8.2	Yes	9.5
20	M	5.8	Cranial nerves	No	TMZ + XRT	–	54	3	SD	Yes	3.9	Yes	4.4
21	M	16.6	Cranial nerves, hemistenia	Yes	TMZ + XRT	oral VP16	54	8	PR	Yes	5.6	Yes	9.7
22	F	13.0	Headache, cranial nerves, emesis			oral VP16	54	3	SD	Yes	11.4	Yes	13.6

Table 1 (continued)

Pt	Sex	Age at diagnosis	Symptoms at diagnosis	Surgery	Treatment	Other treatment	XRT dose	Symptoms delay (weeks)	Response after XRT	Progression	PFS	Death	OS
23	M	14.3	Gait, hemistenia	Yes+ VCS	TMZ + XRT								
				No	TMZ + XRT	Re-irradiation+ oral VP16+ vinorelbine	54	2	PR	Yes	7.9	No	18.0
24	F	3.7	Headache, emesis	No	TMZ + XRT	–	54	6	PR	No	9.7	No	9.1

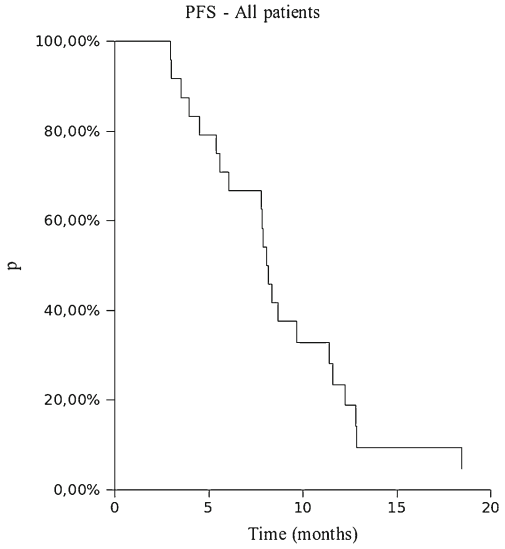

Fig. 1 Kaplan-Meier curve for PFS (all patients)

After progression, most patients withdrew chemotherapy (either TMZ or VCR) and were followed-up in a palliative care setting, when possible at home. Different decisions were taken for patients 18, 21, and 22, who started oral etoposide after TMZ discontinuation. Patient 23 received palliative re-irradiation at relapse, followed by oral etoposide; he had good clinical improvement and radiological response. Eight months later, he had a second progression, both radiological and clinical. Etoposide was then discontinued, and the patient has since then received vinorelbine (30 mg/m^2 weekly e.v. administration on day 1, 8, 21 every 28 days), with a radiologically stable disease for 3 months.

Discussion

In the last decades, pediatric neurooncology patients have benefited from important scientific and clinical progress.

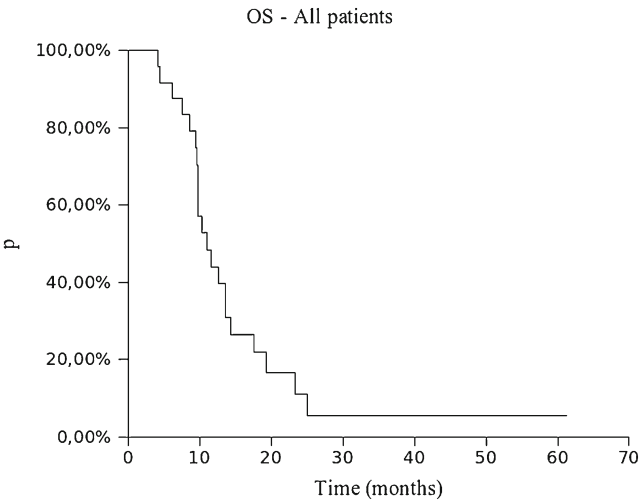

Fig. 2 Kaplan-Meier curve for OS (all patients)

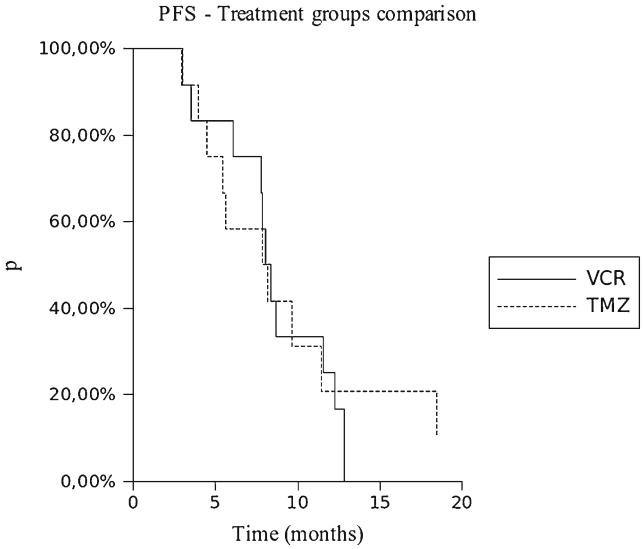

Fig. 3 Kaplan-Meier curve for PFS (VCR vs. TMZ). No statistically significant difference was evidenced between the two groups (Log-rank test p value=0.68)

Advances in neurosurgery, neuroradiology, radiotherapy, and medical oncology allowed obtaining improvements in survival rates and quality of life for the majority of patients.

Such considerations do not apply to DIPG, which is still the most challenging disease for pediatric neurooncologists. DIPG patients almost invariably die.

Multiple treatment modalities have been experimented over many years, but little or no improvements of OS and PFS have been achieved, so far. Radiotherapy is still the only effective treatment; albeit not curative, it delays tumor progression and death.

Chemotherapy intensification did not provide encouraging results. Frappaz et al. achieved a relatively long median OS (17 months) in a study encompassing neoadjuvant high-dose methotrexate, BCNU, cisplatin, and tamoxifen given until progressive disease occurred, then followed by radiotherapy [8]. However, the long-term survival was poor, with a 3-year OS of 4 % and such treatment schedule caused therapy-related toxicity and prolonged hospitalization.

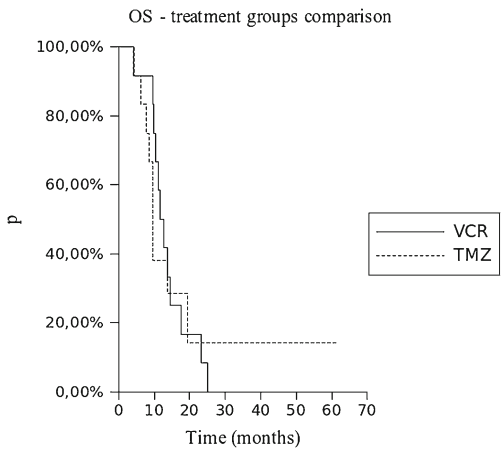

Fig. 4 Kaplan-Meier curve for OS (VCR vs. TMZ). No statistically significant difference was evidenced between the two groups (Log-rank test p value=0.92)

At our center, patients with DIPG have been treated with radiotherapy followed by adjuvant low-dose chemotherapy with either vincristine or temozolomide, in order to give little or no toxicity. Furthermore, we have tried to treat them in the outpatient setting or in day hospital, avoiding hospitalization, as far as possible.

Only two patients in our cohort underwent biopsy. In DIPG, MRI findings are typical (pontine infiltrative lesion hypodense in T1 and hypertense in T2, with mass effect on the surrounding structures), thus histologic confirmation is not necessary and biopsy is rarely performed [1]. Nonetheless, in the latest years, the consensus has been changing due to the possibility to perform stereotactic biopsy safely and to the urgent need for a better understanding of the biology of DIPG. Obtaining genomic information at diagnosis might allow discovering oncogenic mutations, to develop new target drugs, and, in the near future, will hopefully provide patient-specific treatments [5, 17, 23].

Among our patients, outcome was substantially in line with data from other retrospective mono- and multi-institutional series [2, 10, 14, 19].

Data are also coherent with two major systematic reviews published in 2006 and in 2012 [11]. In the systematic update by Jansen et al. [11], the median PFS ranged from 3 to 10 months, while OS ranged from 4 to 17 months.

In our cohort, differences in outcomes (OS and PFS) were not significant between the two groups of patients (VCR vs. TMZ). Only three of our patients are currently alive; patient 23 and 24 have had a short follow-up, being the last two diagnosed cases. Patient 18 has achieved a long PFS and OS (much longer than 24 months), albeit he had disease relapse after 47 months of continuative complete remission. Afterwards, he started therapy with oral etoposide, currently ongoing. This patient's long survival might be related with the long latency of symptoms before diagnosis (headache for more than 3 months), which might indicate a less aggressive tumor biology.

In one case (patient 23), we decided to perform palliative re-irradiation at disease progression. The patient benefited from this therapy, being able to be cured at home with satisfactory quality of life, with a clear improvement of symptoms. Such secondary response lasted for 7 months, then the patients suffered from disease progression again. Re-irradiation was recently described as a reasonable option for palliation of symptoms. The patients who may benefit most from re-irradiation are those with a prolonged response to initial RT, a long interval since initial therapy, and good performance status [7].

The identification of the best treatment strategy for patients with DIPG is still a challenge. None of the chemotherapy schedules used so far has demonstrated clear advantages over the others. Radiotherapy is still the mainstays of treatment, although it delays disease progression only transiently. The possibility of safe surgical tumor sampling has opened the way to wider investigations for a better understanding of the biology of DIPG. Such results are eagerly awaited, along with more effective strategies for the treatment of this devastating disease.

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None of the Authors has financial conflicts of interest. We declare that this manuscript is original, has not been published before, and is not currently being considered for publication elsewhere. The manuscript has been read and approved by all named authors.

The study has been performed in accordance with the 1964 Declaration of Helsinki and its later amendments. All patients, or their parents when needed, gave their informed consent prior to their inclusion in the study.

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