Treatment of childhood diffuse brain stem tumors: comparison of results in different treatment modalities

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Background. Diffuse brainstem tumors in children are rare and its treatment is controversial. Although radiotherapy (RT) used to be the treatment of choice, results remained unsatisfactory. The association of RT with other therapies is common, but lacks scientific data regarding its efficacy. Comparison of results of irradiation alone versus combined treatment modalities is crucial in improving survival.

Method. The authors reviewed twenty-four patients with diffuse brainstem tumors, with mean age of 7 years, treated from December 90 to November 99, at the University of Sao Paulo, Brazil. These patients were subdivided in four groups according to the treatment option at the onset of symptoms. Four patients were treated with radiation alone (total dose of 50 Gy to 62.4 Gy), 6 patients with chemotherapy and radiation, 8 with tamoxifen and radiation and 6 with tamoxifen, radiation and chemotherapy. The results of the different groups were them compared.

Findings. Clinical response was observed in 83.3% of our children, briefly followed by progressive disease. Mean survival was 17 months with no statistically significant differences among the groups. Four patients were alive at the end of the study, with a mean survival of 32.4 months, all of them received combined therapy, but with no statistically significant differences.

Conclusions. Neither the association of radiation therapy with chemotherapy, tamoxifen nor both have showed survival improvement. The prognosis of these patients remains very poor and only investigational trials would justify a highly aggressive approach.

Key words: brain stem tumors, children, radiotherapy, hormone therapy, chemotherapy.

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INTRODUCTION

The brainstem is one of the most important structures in the brain. Comprising several midline diencephalic nuclei, long tracts from cerebral hemispheres, tracts from the cerebellum, nuclei from the cranial nerves, the reticular activating system and vital functional centers, its significance can not be overstated. Treatment of tumours in this region have always posed itself as a special challenge to the medical community.

Brainstem tumors are classified according to their location, extension and contrast enhancement on computed tomography scans (CTS) or magnetic resonance images (MRI). Lesions involving the pons, extending into the midbrain or to the medulla or both are classified as diffuse brainstem tumors (DBT).

DBT in children are rare, accounting for only 1.4% of all tumours, 7-10% of all brain tumours, and approximately 30% of posterior fossae tumours[1-3] in this age group.

The age of diagnosis usually ranges from 6 to 10 years old. The typical symptoms include ataxia, cranial nerves palsy, and hemiparesis, with the later one sometimes developing in a fulminate manner; multiple symptoms are seen in 70% of patients[4].

The duration of symptoms on DBT before diagnosis is shorter in children (2 to 3 months) than in adults (10.6 months)[2]. This is usually associated with a worse prognosis (5-year survival rate of 16% in children compared to 47% in adults). Nevertheless, intervals longer than 2 months from the onset of symptoms until diagnosis, are associated with better survival rates[4].

Biopsy series demonstrated that the proportions of low grade and malignant astrocytomas are roughly equal. Although the proportion expected for autopsies series would be the same, they are not; 60% to 80% of the cases showed anaplastic astrocytomas or glioblastomas, even with low grade tumors formerly con-

firmed by biopsy. These changes may identify either malignant transformation during the progression of the disease or post radiation, or malignant components that were not identified on former biopsies. Histological diagnosis other than the above mentioned were rare[5]. A high risk of complications is associated with the biopsy procedure (10% of severe/fatal). Since this procedure rarely modifies treatment or prognosis, patients are not generally submitted to biopsy[6,7].

The established treatment for DBT has traditionally been the use of external beam irradiation, with doses of 54 to 60 Gy, (1.8 Gy/day)[2]. Patients with untreated diffuse pontine tumors have median survival of 3.9 months while irradiated patients have median survival of 8.8 months. Clinical improvements were observed in 70% of these patients[8,9].

Alternative schemes of hyperfractionated radiotherapy, combined treatment with chemo-radiation or tamoxifen have been studied for DBT. Until now, none of them has demonstrated better results than radiation alone[10,11].

The low incidence of DBT and the toxicity associated with the different treatments make it difficult to establish the best therapeutic option. Over the last decade, several treatment protocols were used at our institution. Their results, compared in a retrospective analysis, are presented in this report.

METHODS AND MATERIALS

From December 1990 until November 1999, 24 children with DBT, considered inoperable by the Neurosurgery Department, were treated in the Radiotherapy Department and Children's Institute of the University of Sao Paulo, Brazil. All children were younger than 14 years.

MRI was the definitive diagnosis exam for the establishment of tumor type and extension. No surgery (except for shunts) or biopsy were performed in these children.

Initially proposed treatment included radiotherapy alone or combined with tamoxifen or chemotherapy. There was no selection criteria for the addition of chemotherapy or tamoxifen, except the use of the current institutional protocol. On all cases, palliative chemotherapy was used after local relapse in patients with good or regular general condition. All children completed the whole radiotherapy treatment.

Patients were divided in 4 main groups, according to received treatment:

Group 1: radiotherapy alone (4 patients);

Group 2: radiation and chemotherapy (5 patients);

Group 3: radiotherapy and tamoxifen (TMX) (9 patients);

Group 4: radiotherapy, tamoxifen and salvage chemotherapy (6 patients).

Radiotherapy was delivered with a megavoltage equipment (linear accelerator or Cobalt unit), total dose ranging from 50 to 62 Gy (median 56.7 Gy) in single daily fractions of 1.8 Gy (5 fractions/week).

On the tamoxifen protocol, the drug was given on the eve of radiation and during radiotherapy (300 mg/m^2, with maximal dose of 450 mg, divided in tree equal doses, per oral), followed by a maintenance dose during the next 52 weeks (200 mg/m^2/day, with maximal of 300 mg/day, divided in two times a day, per oral).

In cases of tumor progression salvage chemotherapy was administered with, Carboplatine 250 mg/m^2, i.v.; and/or Vincristine, 1,5 mg/m^2, i.v., with the suspension of the tamoxifen when still in use, resulting in groups 2 and 4.

The following parameters were studied: gender, age, number and duration of symptoms ($\leq$ 3 months or $>$ 3 months), extension of disease (2 or more sites), total dose (54 Gy or less and $>$ 54 Gy), daily fraction (1.8 Gy or other fractionation), duration of treatment (6 to 8 weeks or more than 8 weeks), clinical and radiological response, and survival.

Response was analyzed by means of clinical and radiological periodical controls. Improvement of symptoms and/or radiological tumor regression of at least 50%, were considered as good responses. Survival was counted from the date of diagnosis until the last follow-up or death.

Statistical analysis

Treatment groups 2, 3 and 4, for the purpose of statistical analysis, were considered as a single group (radiotherapy plus either tamoxifen and/or chemotherapy) and compared to group 1.

Categorical and non-categorical variables, as described above, were analyzed. Gender, age, number (1 or more) and duration of symptoms ($\leq$ 3 months or $>$ 3 months), extension of disease (2 or more than 2 involved sites), were considered as clinical parame ters. Total dose (54 Gy or less and $>$ 54 Gy), daily fraction (1.8 Gy or other fractionation), duration of treatment (6 to 8 weeks or more than 8 weeks), and clinical and radiological response were considered as treatment parameters. Survival was considered the end point.

Data was analyzed using Student-t test, Pearson Chi-square, and Kaplan-Meier with *log-rank* test survival curves. Significance level of at least 5% ($p \leq 0,05$) was assumed, with a 95% confidence interval. SPSS (Statisical Package for Social Science) software was used for calculation[12].

RESULTS

There were 8 boys and 16 girls, (male female ratio 1: 2), with age ranging from 1 to 14 years (mean of 7

TABLE 1. **Distribution of patients according to treatment group**

	RT	RT + CT	RT + TMX	RT + TMX + CT	Total
Number of patients	4	6	8	6	24 (100%)
Male	1	2	2	3	8 (33.3%)
Female	3	4	6	3	16 (66.6%)
Mean age (years)	5.5	7.7	5.9	8.8	6.9
Median age (years)	5.5	5.5	5.5	8.5	5.5
> 1 symptom	3	6	8	5	22 (91.6%)
Extension					
≤ 2 sites	3	4	2	2	11 (45.8%)
> 2 sites	1	2	6	4	13 (54.2%)
Improvement	3	5	6	6	20 (83.3%)
Total dose					
≤ 54 Gy	2	3	5	6	16 (66.6%)
> 54 Gy	2	3	3	0	8 (33.3%)
Dose/fraction					
1,8 Gy	4	5	7	6	22 (91.6%)
other	0	1	1	0	2 (8.4%)
Duration of treatment					
6-8 weeks	3	4	7	4	18 (75.0%)
> 8 weeks	1	2	1	2	6 (25.0%)
Duration of symptoms*					
≤ 3 months	4	4	5	5	18 (75.0%)
> 3 months	0	3	3	1	6 (25.0%)
Mean survival (months)	17	28.17	9.75	13.17	17
Median survival (months)	14	13	7	11	12

*0.7 to 16 months. RT: radiotherapy; CT: chemotherapy; TMX: tamoxifen.

years). The common neurological signs and symptoms at presentation were ataxia, cranial nerves palsies, long tract signs, and increased intracranial pressure. Multiple symptoms were observed in 22 children (96%).

Diffuse pontine lesions infiltrating other brain stem segments, as far as the thalamus, the cerebellopontine peduncle or the cerebellum, were the most frequent presentations. Table 1 presents patients characteristics according to groups.

Twenty-two patients (92%) presented with more than one symptom. Eighteen (75%) patients had symptoms that appeared 3 months or less before diagnosis and 20 (83%) received combined treatment. Analysis of categorical data of different treatments versus gender, number or duration of symptoms revealed no statistical differences between the groups. Comparison of disease extension was also equal between the groups. 18/24 (67%) patients completed treatment within 8 weeks and 83.8% (20/24) had clinical and/or radiological improvement. Also, no statistically significant differences between the groups was found.

The studied parameters were also individually compared among the treatment groups: radiation alone (RT), radiotherapy plus chemotherapy (RT with CT), radiotherapy plus tamoxifen (RT with TMX) and radiotherapy plus tamoxifen plus chemotherapy (RT with CT and TMX) and revealed the following:

Immediate improvement of symptoms and neurological function (even during irradiation) was observed in 84% of the children compared to 70% in previous series[15]. Partial response was observed in all patients, most of them with residual disease at MRI. A few presented cystic or fibrotic images, which could not be considered for sure as complete response.

Tumor extension showed no significant differences among the treatment groups, except for patients who received TMX vs those who did not ($p = 0.05$). Fourteen patients received TMX, 10 (71.4%) had extensive disease, i. e., more than 2 involved sites. Seven out of 10 (77%) patients who did not receive TMX had smaller tumors, confined to 2 sites only.

Mean survival was 17 months. Children who presented symptoms for less than 3 months before diagnosis had a median survival of 10 months, against 16 months for the others ($p = 0.7$). Neither the clinical parameters (gender, age, number of symptoms, duration of symptoms and extension of the disease) nor the technical parameters (total dose, daily fractions, duration of radiotherapy, and clinical and radiological response) had influenced survival. Four patients were alive with a mean follow-up of 54.2 months (range: 4 to 104 months). All of them received combined treatment: RT and TMX (3 patients) and RT and CT (1 patient). Radiation dose was greater than 54 Gy in 3 of these patients.

The mean survival time according to treatment was also studied. Correlation of radiation dose, CT and TMX with survival showed no statistically significant differences in any of the studied groups. Analyzing

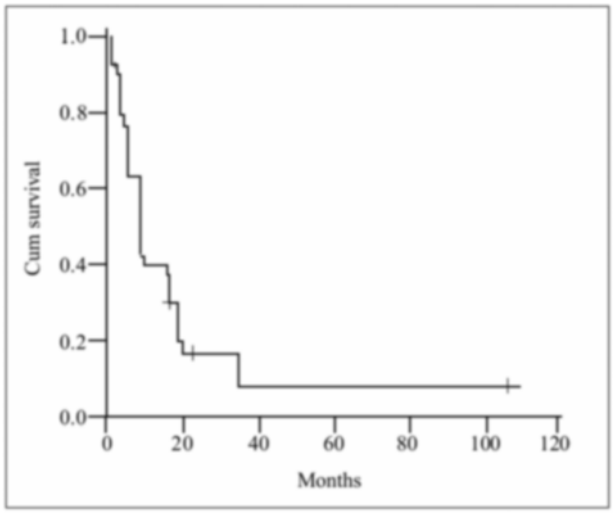

Fig. 1. Overall survival.

the survival considering the different treatment combinations, also no statistically significant differences were found. Figure 1 presents overall survival for all groups.

DISCUSSION

Diffuse brain stem tumors are rare and have a very poor outcome, with 3.9 months median survival for untreated patients and 9 months for irradiated patients. Prognosis is based mainly on age, disease extent and duration of symptoms[5,6].

In our study, all patients had diffuse brain stem tumors and less than 14 years. Radiation therapy was offered as the main treatment option, associated or not with other therapeutic alternatives. Clinical response was observed in 84% of our population compared to approximately 70% in other series[9], and briefly followed by signs of progressive disease.

In this series, children with symptoms for more than 3 months had a survival benefit greater than 50% as compared to the group whose symptoms duration was less than 3 months. None of the studied parameters were correlated to outcome. This may characterize a less aggressive and slow growing tumor associated with longer duration of symptoms. Similar correlation was observed in larger trials, which we considered not comparable with our results, since all types of brain stem tumors were included in these studies, not only the diffuse ones, whose prognosis are even worse[9,14].

At least 3 of the 24 analyzed children presented long term survival. They received combined treatment, but when compared to radiation alone, no differences were observed. The only significant factor associated to treatment was related to patients who did or not receive TMX. A larger number of patients with most extensive disease had TMX combined in their treatment.

Since this is a retrospective study, probably a bias was created in survival analysis correlated with treatment: children with bad prognostic factors received more aggressive treatment.

Treatment of diffuse brain stem tumors is not yet well defined. The bad prognosis correlated to the disease leads to the use of many therapeutic alternatives, in order to improve local control and survival.

Hyperfractionated radiotherapy, at first, showed promising results, but failed to demonstrate survival improvement. The Pediatric Oncology Group compared 54 Gy (1.8 Gy/day) with 70.2 Gy (1,17 Gy bid). No differences in survival were observed between the 2 groups[10,15]. Neither the association with chemotherapy nor high-dose tamoxifen showed improvement in quality of life and survival. Until now, treatment options for children with brain stem tumors are still associated with very poor outcome[16-18].

In a pilot study, 32 children with diffuse brainstem gliomas received escalating doses of beta-interferon during and up to 6 weeks after the end of hyperfractionated RT at a dose of 72 Gy. Long-term survival remained less than 10%. No benefit was observed[19].

The use of temozolomide, an oral alkylating agent that penetrates the blood-brain barrier, inspired numerous investigational trials in brain gliomas. Despite the initial enthusiasm, the impact of temozolomide in pediatric, either progressive low grade or high grade gliomas, remains to be demonstrated[20-22].

In a recent study of Broniscer et al, children with newly diagnosed diffuse brainstem gliomas received conventionally fractionated radiotherapy followed, 4 weeks after radiation, by 5-day temozolomide for a total of 6 cycles. The association of temozolomide in these patients did not alter their poor prognosis. All died of progressive disease, with median survival of 12 months[23].

Median survival of 12 months, with mean survival of 17 months observed in our patients may be considered quite better than other reports, which also consider both diffuse and localized brain stem tumors. Although not significant, children treated with higher doses of radiotherapy, or who were selected for CT or did not receive TMX, presented better mean survival time than the other groups. However, patient selection could explain these results, where children with better performance status and smaller tumors presented a better outcome.

Our results indicate that irradiation alone of diffuse brain stem tumors may achieve, at least, similar outcome of those patients treated with associated modalities. No benefits were observed with combined treatment when compared to radiation alone. The indication of combined RT and TMX was significantly higher in more extensive disease and was used in most of the

long-term survivors. Perhaps, the small number of patients impaired the achievement of statistical significant differences among the other analyzed parameters.

The very poor prognosis of children with diffuse brain stem tumors invites the use of novel approaches, which include more aggressive treatment programs. Since improvement of symptoms can be obtained with standard radiotherapy, and no survival benefit has been demonstrated, until now, with other strategies, it is obviously important to avoid jeopardizing the quality of life in the few months following treatment. New strategies are needed, but still investigational.

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