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Pediatric Brainstem Glioma: A Review

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Abstract
Brainstem gliomas are heterogenous group of tumors with varying biological behaviour. They share a major part in causing brain tumors related deaths in paediatric patients. A large number of trials have been done so far with the use of different radiotherapy regimes and the use of different chemotherapeutic agents with a view to improve the overall survival but no statistical significant survival impact has been attained. The median survival is generally one year[11].
Keywords: *Paediatric brainstem glioma .overall survival. radiotherapy.*

Introduction

Brainstem gliomas include tumors arising in midbrain, pons and medulla oblongata and account for 15 to 20% of all CNS tumors in children[1]. They range from low grade focal, dorsal exophytic, cervicomedullary to the most aggressive one which is diffuse interstitial pontine glioma (DIPG). Median age at onset is 6.5 years and survival is generally about 12 months[1]. The prognosis and overall survival of tectal and midbrain glioma is comparatively better among other sites in brainstem[11].

Table 1[11]

Location	Percentage of cases in study	5 year overall survival
Medulla	18	53
Pons	59	29
Midbrain	14	100
Medulla	9	83

Gliomas are most common CNS tumors in childhood and they have a diverse variation in their location which affect the prognosis drastically. So far many trials have been performed to explore the role of chemotherapy in Brainstem Gliomas but still Radiation Therapy remains the standard of care.

Methods and Material

We did a detailed analysis of articles on paediatric brainstem gliomas from PUBMED discussing about altered fractionation regimes and use of concurrent and adjuvant and neo adjuvant chemotherapy in brainstem gliomas. Majority of them were Phase 2 or Phase 3 trials. Patients generally had history of onset of brainstem syndrome since 3 months .Symptoms of brainstem syndrome included Cranial nerve deficit, long tract signs and ataxia .Patients with lesion in midbrain generally had symptoms of raised intracranial pressure (ICP) due to hydrocephalus due to anatomical proximity to aqueduct of sylvius[11]. T1w and T2w MRI images were used for diagnosis as on CECT scan only 0 to 25% of tumor volume on an average shows enhancement[12] and biopsy is a highly morbid procedure in these cases.

Table 2[11]

MRI characteristics	Percentage of patients(%)
Dorsal exophytic	45
Hydrocephalus	41
Cystic	51
Contrast enhancement	60
Basillar artery engulfement	25

Radiotherapy is the definitive management for these patients. Chemotherapy has been tried as an adjuvant treatment for these patients in various trials .Conformal radiotherapy has been used in all cases.

Discussion

Brainstem glioma is an MRI based diagnosis using both T1W and T2W images .In these studies no performance status was calculated .In all the studies having two arm the patients were randomly assigned to any group. The conventional fractionation regime used is 54 Gray in 30 fractions. Two hypofractionation regimes employed were 39 Gray in 13 fractions (3 Gray per fraction) and 44.8 Gray in 16 fractions (2.8 Gray per fraction) In this study other than steroids no any chemotherapeutic drug was used and skin toxicity was assessed on the basis of RTOG guidelines[4]. No difference in median overall survival between both hypofractionation and conventional regime was obtained (9 months Vs 9.4 months) and time to progression (5 months Vs 7.6 months)[4]. Hypofractionation has advantage of reducing the total hospital stay of the patient and reducing patient load in hospital.

One other study exploring the role of hypofractionation was two arm study .Equal number of patients were included and randomized in both the arms. The hypofractionation arm was given a dose of 39Gy in 13 fractions .Median overall survival was 9.5+_ 1 months. The other arm was treated with conventional dose of 55.8Gy in 31 fractions. There the median overall survival was 9.9+_1 months[7].

The hyperfractionation regime used in other study was to give 2 fractions of 117cGy per day to a total of 7020cGy. The other arm in which conventional fractionation was used was given 4 cycles of neoadjuvant cisplatin (100mg/m2) and cyclophosphamide (3g/m2). Morbidity was similar in both the arms and hyperfractionation did not improve either event free survival (p=0.96) or the OS (p=0.65)[2].

Other hyperfractionation regime included patients in the age group of 3 to 21 years and were treated with a twice daily dose of 1.26Gy per fraction with a gap of 6 hours between two fractions to a total dose of 75.6Gy in 60 fractions in 6 weeks. The median overall survival was found to be 10 months (p=0.46)[5].

The use of chemotherapeutic agents in other study included the use of concurrent TMZ (75mg/m2) for 6 weeks with radiotherapy followed by adjuvant TMZ (250mg/m2) for 5 days and cis RA(100mg/m2/day) for 21 days in a 28 days cycle and this was continued till MRI was suggestive of disease progression.MRI Brain was done 2 months after the completion of radiotherapy and the rafter 3 monthly. Overall survival was of 9.15 months[8].

The other study of utilising concurrent and adjuvant TMZ as the previous study but with the metronomic dose of 85mg/m2 in both concurrent and adjuvant setting. The median overall survival

was 9.8 months. The study concluded that the use of metronomic dose of TMZ did not bring any statistical improvement in overall survival of these patients[14].

The role of other chemotherapeutic agents like Lomustine, Cisplatin, Cyclophosphamide, Vincristine have also been explored but without a statcically significant improvement in overall survival[15].

Review Process

STUDY	TYPE	TOTAL PATIENTS=n	TREATMENT	MEDIAN OVERALL SURVIVAL	Reference number
Radbourt University Medical Centre Nijmen	Matched Cohort Analysis	16	39Gray in 13 fractions (hypofractionation)	9 months(8 – 11 months)	4
Erasmus Medical Centre Rotterdam	Matched Cohort Analysis	10	44.8Gray in 16 Fractions (hypofractionation)	9 months(8 – 11 months)	4
Pediatric Oncology Group (POG)	Phase III Trial (conventional Vs Hyperfractionation)	133	54Gray in 30 fractions (arm 1 n=66) 70.20 Gray (117cGy per fraction with2 fractions per day) Concurrent cisplatin(100mg/m2 continuous infusion)on day 1,week 3,week 5 in both arms	8.5 months	2
Kretchma et al	Phase 2 trial	37	Cisplatin+Cyclophosphamide followed by RT(66Gray in 60 fractions)(Hyperfractionation)	9 months	13
Jalali et al	Phase 2 trial	20	TMZ+RT(conventional) followed by TMZ	9.15 months	8
Sharp et al	Phase 2 trial	15	TMZ+RT(conventional)	9.8 months	14
Jenkin,et al	Phase 2 trial	Only RT=35 RT+CT=39	RT followed by lomustine,VCR and prednisolone Vs only Radiotherapy	5 year overall survival RT=17% RT+CT=23%	15

Conclusion

Brainstem gliomas have poor prognosis and the use of conventional radiation fractionation and chemotherapy shows no added advantage over hypofractionation regime or hyperfractionation regime.

References

1. Hargrave D, Bartels U, Bouffet E. Diffuse brainstem glioma in children: critical review of clinical trials. Lancet Oncol.2006;7(3):241–8.
2. Mandell LR, Kadota R, Freeman C, et al. There is no role for hyperfractionated radiotherapy in the management of children with newly diagnosed diffuse intrinsic brainstem tumors: results of a Pediatric Oncology Group phase III trial comparing conventional vs. hyperfractionated radiotherapy. Int J Radiat Oncol Biol Phys. 1999;43:959–964. [PubMed]
3. Chassot A et al. Radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. J Neurooncol. 2012;106(2):399–407. No benefit was found from the addition of TMZ to RT for the treatment of DIPG.
4. Janssens GO et al. The role of hypofractionation radiotherapy for diffuse intrinsic brainstem glioma in children: a pilot study. Int J Radiat Oncol Biol Phys. 2009;73(3):722–6.
5. Freeman CR, Krischer JP, Sanford RA, Cohen ME, Burger PC, Carpio R, et al. Final results of a study of escalating doses of hyperfractionated radiotherapy in brain stem tumors in children: a Pediatric Oncology Group study. *International*

Journal of Radiation Oncology, Biology, Physics 1993;27(2):197-206

6. Kretschmar CS, Tarbell NJ, Barnes PD, Krischer JP, Burger PC, Kun L. Pre-irradiation chemotherapy and hyperfractionated radiation therapy 66 Gy for children with brain stem tumors. A phase II study of the pediatric oncology group, protocol 8833. *Cancer* 1993; 72(4):1404-13.
7. Ahmed S, Zaghloul MS, Eldebawy E. Hypofractionated radiotherapy for pediatric diffuse intrinsic pontine glioma (DIPG) [O128]. *Pediatric Blood and Cancer* 2012;59(6):1003.
8. Jalali R et al. Prospective evaluation of radiotherapy with concurrent and adjuvant temozolomide in children with newly diagnosed diffuse intrinsic pontine glioma. Int J Radiat Oncol Biol Phys. 2010;77(1):113–8.
9. Sharp JR et al. A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma. Eur J Cancer. 2010;46(18):3271–9.
10. Survival rates and prognostic predictors of high grade brain stem gliomas in childhood:a systematic review and meta-analysis Hadeel Hassan1,2 · Anne Pinches Susan V. Picton2 · Robert S. Phillips
11. Brainstem Glioma: A Review Sean A. Grimm & Marc C. Chamberlain
12. Bartels U et al. Proceedings of the diffuse intrinsic pontine glioma (DIPG) Toronto Think Tank: advancing basic and translational research and cooperation in DIPG. J Neurooncol. 2011;105 (1):119–25. This is a transcript of a meeting of DIDG experts that discusses state-of-the-art treatment and basic/translational research in the field.
13. Kretschmar CS et al. Pre-irradiation chemotherapy and hyperfractionated radiation therapy 66 Gy for children with brain stem tumors. A phase II study of the Pediatric Oncology Group, protocol 8833. Cancer. 1993;72(4):1404–13.
14. Sharp JR et al. A multi-centre Canadian pilot study of metronomic temozolomide combined with radiotherapy for newly diagnosed paediatric brainstem glioma. Eur J Cancer. 2010;46(18):3271–9.
15. Jenkin RD et al. Brain-stem tumors in childhood: a prospective randomized trial of irradiation with and without adjuvant CCNU, VCR, and prednisone. A report of the Childrens Cancer Study Group. J Neurosurg. 1987;66(2):227–33.