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[11]. 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.

| 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[17].

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

**Review Process**

| STUDY                      | TYPE                         | TOTAL PATIENT S=n | TREATMENT                                      | MEDIAN OVERALL SURVIVAL | Reference number |
|----------------------------|-------------------------------|-------------------|-----------------------------------------------|--------------------------|------------------|
| Radbourt University Medical Centre Nijmegen | 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.

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