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High Grade Gliomas: Newer Horizon-New Hope

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Abstract: ***Objective: Malignant Gliomas are the most aggressive cancers producing severe and progressive disability,usually leading to death. The standard treatment consists of Cytoreductive Surgery followed by Radiotherapy and Concurrent Temozolomide and Adjuvant Temozolomide. Optimizing the adjuvant chemotherapy regime is one potential strategy for improving survival and Quality of life Methods: In this study, 40 diagnosed patients of high grade gliomas,who underwent resection, received concurrent chemoradiation and adjuvant chemotherapy were analysed. [25 pt's- Anaplastic Astrocytoma (Gr III) ,13 pt's- Glioblastoma Multiforme (GBM) & 2 pts-Gliosarcoma]. Patients received concurrent Temozolomide 75 mg/m2 daily for 42 days. Weekly Hematological and Biochemical investigations were done. 4 weeks after chemo-irradiation, patients received Adjuvant Temozolomide-150 mg/m2 days 1 to7 and days 15 to 21 for every 28 days for 6 cycles. Investigations were done every 2weeks (Hematological and Biochemical parameters were assessed). Response rate, survival outcome, recurrence rates & toxicities were analyzed. The response was assessed with CT/MRI every 3 monthly from the time of completion of treatment. Results: The overall survival in high grade glioma was 38.3 months. In Anaplastic astrocytoma (Gr III), maximum survival was 44 months and in Glioblastoma multiforme it was 26.6 months. The survival between the grades is significant with 'p' value of 0.001, significant better 2year OS was seen in AA (Gr III). There were 10 deaths due to disease progression, out of which 8 cases were GBM and 2 cases were AA (Gr III). 18 pt's developed Gr-III Thrombocytopenia and 16 patients had Leukopenia (Gr I-II).None of the patients developed Gr-IV hematological toxicities. Nausea and vomiting (Grade 1-2) was seen in 80% of the patients. Conclusion: Dose dense regimen has a role in terms of efficacy than the adjuvant treatment of standard dose of 200 mg/m2 days 1 to 5 for every 28 days cycle for 6 months. The toxicity is increased with majority being Grade I, II leucopenia and Grade III Thrombocytopenia***

Keywords: High Grade Glioma, Anaplastic astrocytoma, Glioblastoma multiforme, Temozolomide, MGMT- O6 methyl guanine DNA methyl transferase

1. Aim

Malignant Gliomas are the most aggressive cancers producing severe and progressive disability, usually leading to death. Due to the infiltrating nature of disease it is difficult to obtain complete resection. It is challenging to the Oncologists to improve the Survival in high grade glioma patients. The standard treatment consists of Cytoreductive Surgery followed by Radiotherapy and Concurrent Temozolomide (TMZ) and Adjuvant Temozolomide.(1)

2. Background

High grade gliomas are the most common primary brain tumours and accounts for 60-70% of all CNS tumours in adults (2). Despite advances in therapy, these tumours are associated with poor prognosis. Inspite of all the newer techniques of treatment in High Grade Gliomas, prognosis still remains poor with a median survival time of 14.6 months in patients receiving Radiotherapy (RT) with Temozolomide v/s 12 months in patients receiving Radiotherapy alone.

Indian council for Medical Research-2009 report of the cancer registry survey conducted on glioma incidence in India revealed 5.8% in Mumbai, 6.7% in Bangalore, 3.5% in Chennai, 5.6% in Dibrugarh and 28.2% in Trivandrum among males and 6.3% in Mumbai, 5.6% in Bangalore, 7.5% in Chennai, 0% in Dibrugarh and 21.8% in Trivandrum among females(3).

Optimizing the Adjuvant chemotherapy regimen is one potential strategy for improving patient outcomes. Successful strategies have included combinations of chemotherapy, dose intensification & alternate drug delivery schedules. A meta analysis including different chemotherapeutic agents and regimes has shown prolonged survival and delaying recurrences than RT alone in glioma patients(4). Recent EORTC 26981/22981 and NCIC CE3 Randomised phase 3 trial has proved the efficacy of temozolomide when administered concomitant and sequential to post-op radiotherapy in newly diagnosed Glioblastoma through standard dosing (Stupp's regimen) (5).

One barrier to successful treatment of Glioblastoma is resistance to alkylating agents like Temozolomide. It is one of the second generation Imidazotetrazinone prodrug which converts into active metabolite,it acts by inducing DNA damage by forming O6-methyl guanine DNA adducts(6). O6-methyl guanine DNA methyl transferase (MGMT) is a DNA repair enzyme which maintains the genomic integrity by removing the alkyl group from O6-guanine, making it the primary mechanism of resistance to temozolomide. As MGMT is a suicide enzyme,it could,in theory,be depleted if the rate of alkylation of DNA outpaces the rate of MGMT protein synthesis for DNA repair.

The dose dense regimen in adjuvant scenario, has shown some efficacy even in patients with tumours lacking MGMT gene promoter methylation. Gliomas are associated with a poor prognosis, especially high-grade tumours in older patients. Patients with high-grade gliomas have a better prognosis if they are younger, have a better performance status, have Anaplastic Astrocytoma (Gr III) tumour or if complete resection is achieved. Till date, no trial has compared the different durations of therapy in a randomized fashion. The rationale for maintenance treatment is that residual disease is expected in almost all patients, and it is believed that additional cycles could delay recurrence.

3. Material & Methods

In this study, 40 patients were analysed from May-2011 to April-2015.

Inclusion criteria:

1) Age between 18 and 70 years.
2) Histological diagnosis of WHO grade 3 and 4 glioma patients.
3) KPS more than or equal to 70.
4) Baseline complete hemogram, LFT, RFT within normal limits.

Exclusion criteria:

1) Age less than 18 and more than 70 years.
2) KPS less than 70.
3) Abnormal Baseline complete hemogram, LFT, RFT .

4. Patient's Characteristics

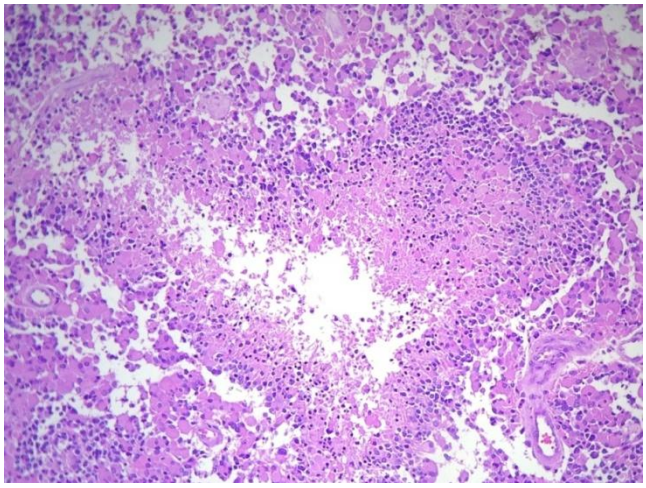
40 newly diagnosed patients of HGG in age group (18-70 yrs), post resection received concurrent chemo-irradiation. [25 pt's- Anaplastic Astrocytoma (Gr III) ,13 pt's- Glioblastoma Multiforme (GBM) & 2 pts- Gliosarcoma]. The Radiotherapy dose delivered was 60Gy/30# by Telecobalt for 14 patients and 26 patients received radiotherapy by Conformal technique. Patients also received Concurrent Temozolomide 75 mg/m2 daily for 42 days. Weekly Hematological and Biochemical investigations were done. 4 weeks after chemo-irradiation, patients received Adjuvant Temozolomide-150 mg/m2 days 1 to7 and days 15 to 21 for every 28 days for 6 cycles[7]. Investigations were done every 2weeks (Hematological and Biochemical parameters were assessed). Response rate, survival outcome, recurrence rates & toxicities were analyzed. The response was assessed with CT/MRI every 3 monthly from the time of completion of treatment.

5. Statistical Analysis

The statistical analysis was done using 'R' software. Survival analysis was done using Kaplan Meier curves. Test of equality of survival distributions for the different levels of Histopathology grade was done using Log Rank test.

Table 1: Patient's characteristics

		No of patients
Age	< 40 years	12
	41-59 years	22
	>60 years	6
Sex	Male	28
	Female	12
Histyology	A.Astrocytoma	25
	Glioblastoma	13
	Gliosarcoma	2
Performance status	Good	30
	Poor	10
Extent of resection	Complete	18
	Incomplete	16
	Biopsy	6



Histopathology: Glioblatoma multiforme- Shows foci of serpentine necrosis with palisading of malignant cells which show nuclear pleomorphism and abundant eosinophilic cytoplasm.

Table 2: Patient's histology details

Case Processing Summary				
Histopathology	Total No.	No. of Events	Censored	
			No.	Percent
Anaplastic Astrocytoma (Gr III)	25	2	23	92.0%
Glioblastoma multiforme	15	8	7	46.7%
Total	40	10	30	75.0%

Overall Comparisons

	Chi-Square	difference	significance.
Log Rank (Mantel-Cox)	10.281	1	**0.001**

Test of equality of survival distributions for the different levels of Histopathology.

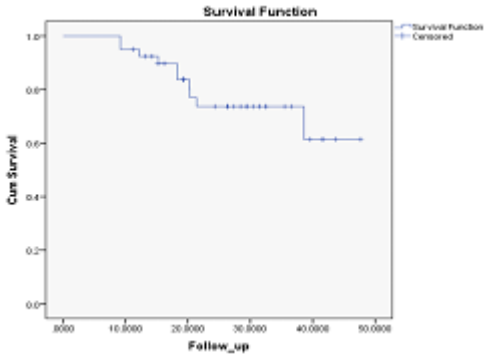


Figure 1: overall survival

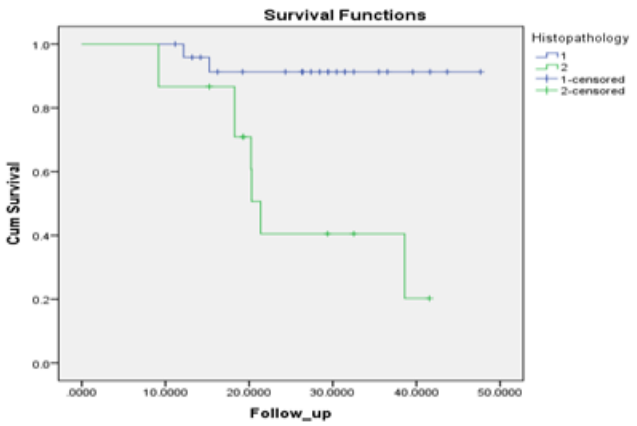


Figure 2: Overall Survival Anaplastic astrocytoma Gr III v/s Glioblastoma multiforme.

6. Results

At the time of analysis, the Overall Survival in High grade glioma was 38.3 months. In Anaplastic astrocytoma (Gr III) maximum survival was 44 months and in Glioblastoma multiforme, it was 26.6 months. The survival between the grades is significant with 'p' value of 0.001, significant better 2year OS was seen in AA (Gr III). There were 10 deaths due to disease progression, out of which 8 cases were GBM and 2 cases were AA (Gr III). Reirradiation was done in 12 patients. 18 pt's developed Gr-III Thrombocytopenia and 16 patients had Leukopenia (Gr I-II).None of the patients developed Gr-IV hematological toxicities. Nausea and Vomiting (Grade 1-2) was seen in 80% of the patients.

7. Conclusion

Dose dense regimen has a role in terms of efficacy than the adjuvant treatment of standard dose of 200 mg/m2 days 1 to 5 for every 28 days cycle for 6 months. The toxicity is increased with majority being Grade I, II leucopenia and Grade III Thrombocytopenia. In Patients developing recurrance, Gliosarcomas are on the rise.

However further randomized studies with higher number of patients and different chemotherapy drugs using different modalities of treatment are necessary to improve the survival outcomes in High Grade Gliomas. Further, the duration of adjuvant therapy must be extended in patients with good KPS for better outcomes.

8. Discussion

The 2-year survival rate of patients with Glioblastoma accrued to research studies increased from 10% to nearly 40% from 2000 to 2010. These improvements began with the demonstration of a survival benefit, when daily temozolomide was administered with 6 weeks of standard radiation and for 6 months thereafter.

The only study that directly compared the 7-days-on/7-days-off regimen with the standard 5-day regimen in the recurrent setting was reported by D'Amico et al[8]. Unfortunately, this was a very small study involving only 20 patients with GBM who progressed after surgery and RT.

The dose used in the 7-days-on/7-days-off regimen was initiated at 50 mg/m2/day and escalated up to 150 mg/m2/day and the investigators reported that this was well tolerated. Median survival was 21 months for patients treated with the 7-days-on/7-days-off regimen versus 14 months for patients treated with the standard 5-day regimen. Although this was a small study, it suggests that the 7-days-on/7-days-off regimen may be more effective.

The adjuvant Temozolomide must be given for atleast 1 year in patients with good KPS. The standard adjuvant Temozolomide duration of 6 months must be extended as good response rates are seen in patients who continued treatment for longer duration. Improving the survival and Quality of life must be given prime importance in High grade gliomas. New drug regimes must be explored taking the patient to newer horizons, giving new hope.

9. Conflicts of Interest

The authors declare that there is no conflict of interests regarding the publication of this paper.

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