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ORIGINAL PAPER

Compliance of temozolamide with concurrent radiotherapy as an adjuvant in patients with high grade glioma – a retrospective study

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ABSTRACT

Introduction and aim. High grade glioma is the most aggressive form of primary brain tumour with a median survival of one year. Maximal safe resection followed by temozolamide-based concurrent chemoradiation and adjuvant chemotherapy is the standard of care. To assess the compliance of temozolamide in patients of high-grade glioma who underwent concurrent chemoradiation followed by adjuvant chemotherapy

Material and methods. 30 patients of high grade glioma diagnosed and treated in our Oncology department during the period of March 2016 to March 2018 were analyzed retrospectively. Cases included in this study were patients with biopsy proven high grade glioma who underwent maximal safe surgery, temozolamide-based concurrent chemoradiation, followed by adjuvant chemotherapy with temozolamide. Data regarding age, gender, histopathology, extent of surgery, performance status, radiotherapy dose, chemotherapy cycles and treatment toxicity profiles were recorded.

Results. Treatment was generally well tolerated with most patients experiencing grade 1 and 2 toxicities, which were managed with supportive care. Grade 3 toxicities were noted as follows: anaemia (6.7%, n=2), neutropenia (16.7%, n=5) and thrombocytopenia (16.7%, n=5). Treatment with TMZ was discontinued in 6.7% (n=2) of individuals due to myelosupression. No grade 4 hematological toxicities were observed in the study group.

Conclusion. The compliance of temozolamide in high grade gliomas is high with less treatment interruptions and manageable side effect profile.

Keywords. glioblastoma multiformae, high grade gliomas, radiotherapy, temozolamide

Introduction

High grade gliomas (HGG) are the most aggressive primary brain tumours. The standard of care for newly diagnosed high-grade glioma includes maximal safe resection of the tumour followed by 6 weeks course of radiotherapy with concurrent temozolamide (TMZ), followed by adjuvant TMZ for 6months. Previous studies proved that postoperative radiotherapy compared to surgery alone provided significant survival advantage.[1,2] A phase III trial by stupp et al showed that temozolamide given concurrently with radiotherapy gives better overall survival than radiotherapy alone in glioblastoma multiforme patients.[3] The European Organisation for the Research and Treatment of Cancer (EORTC) study proved that concurrent TMZ along with radiation followed by Adjuvant TMZ had increased the median

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survival & 2-year survival rate. Another study showed that patients completing 6 cycles of adjuvant TMZ had significantly better outcome.[4]

Temozolamide is an oral second-generation alkylating agent which readily crosses the blood brain barrier and has near 100% bioavailability. TMZ is the prodrug of alkylating agent 5-(3 methyltriazen-1-yl) imidazole-4-carboxamide (MTIC). After administration, TMZ spontaneously hydrolyzes to the active metabolite MTIC & subsequently to the active methylating agent, methyl hydrazine. TMZ exerts its anti-tumor effects by methylating guanine at the N7 (70% of adducts) and O6 (5% of adducts) positions and adenine at the N3 position (9% of adducts).[5,6]

The antitumour activity of the TMZ has been shown in preclinical studies.[7] Currently the recommended dosing schedule for TMZ is 75mg/m2 for concurrent chemoradiation and 200mg/m2 for 5 days every 28 days in the adjuvant setting. Many studies tried different schedules to determine the efficacy without enhancing the toxicity.[8-11] Aforementioned doses were used in this study.

Aim

The aim of the study was to analyze the compliance of the TMZ in patients getting concurrent radiation and followed by adjuvant TMZ in a tertiary care hospital.

Material and methods

Ethical approval

Ethical approval was obtained from the Institutional ethical committee, Government Stanley Medical College and hospital (ECR/131/Inst/TN/2020/RR-21).

Study design

30 patients of high-grade gliomas diagnosed and treated in our Oncology department during the period of March 2016 to March 2018 were analyzed. The cases included biopsy proven high grade glioma patients who underwent maximal safe surgery, postoperative radiotherapy and concurrent temozolamide followed by adjuvant TMZ. Adequate bone marrow reserve, normal renal parameters and hepatic parameters were ensured before the study. Data regarding age, gender, histopathology, extent of surgery, performance status, radiotherapy dose, chemotherapy cycles and toxicity profiles were recorded. Side effects were graded in severity based on CTCAE 4 guidelines.

- Patients receiving transfusions were classified as having grade 3–4 cytopenias during the transfusion period.
- This adjustment was not made for hematopoietic growth factor administration.
- Cytopenias were attributed to concomitant daily TMZ and RT administration if they occurred at any point before thestart of adjuvant TMZ (usually four weeks after the completion of concomitant therapy).
- In patients who developed hematologic toxicity, TMZ administration was delayed, dose adjusted, or discontinued according to the guidelines Additionally, patients developing hematologic toxicity underwent a careful medication review (Table 1).

Table 1. Blood and lymphatic system disorders

	Grade				
Adverse events	**1**	**2**	**3**	**4**	**5**
Anemia*	Hemoglobin (Hgb) <LLN– 10g/dl; <LLN–6.2mmol/L; <LLN–100g/L	Hgb <10.0–8.0g/dL <6.2–4.9 mmol/L; <100–80g/L	Hgb <8.0g/dL <4.9 mmol/L; <80g/L; Transfusion indicated	Life-threatening consequences; urgent intervention indicated	Death
Bone marrow Hypocellular**	Mildly Hypocellular Or <=25% reduction from normal cellularity for age	Moderately Hypocellular Or >25– <50% reduction from normal cellularity for age	Severely Hypocellular Or >50– <=75% reduction from normal cellularity for age	Aplastic persistent for longer than 2 weeks	Death
Febrile Neutropenia***	–	–	ANC <1000/mm3 with a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour	Life threatening consequences; urgent intervention indicated	Death

* A disorder characterized by a reduction in the amount of Hemoglobin in 100 ml of blood. Signs and symptoms of anemia may include pallor of the skin and mucous membranes, shortness of breath, palpitations of the heart, soft systolic murmurs, lethargy and fatigability; ** A disorder characterized by the inability to produce hematopoietic elements; *** A disorder characterized by an ANC <1000/mm^3 and a single temperature of >38.3°C (101°F) or a sustained temperature of ≥38°C (100.4°F) for more than one hour

Radiotherapy and chemotherapy treatment

After maximal safe surgery, postoperative radiotherapy was given at a total dose of 6000cGy in 200cGy per fraction over a period of 6-7 weeks in 2 phases. 5000 cGy was given to the tumour bed/residual tumour along with the surrounding edema with 3cm clearance in the initial phase. Second phase of radiation was administered to tumours with 3 cm margin. The radiotherapy was delivered by two opposing lateral fields with Telecobalt machine. Patients received concurrent TMZ (75mg/m^2/day) 7 days per week one hour before radiation and 6 cycles of adjuvant TMZ (200mg/m^2/day) day 1-5 in every 28 days.

Statistical analysis

Data was entered in MS-Excel (Redmond, Washington, USA) software and analysed by using SPSS version 26 (IBM, Armonk, NY, USA). Descriptive statistics were seen by mean and standard deviation for numerical data, whereas for categorical data, frequency table was represented.

Results

Patients and treatment characteristics

The median age of the study group was 46.7 years (Range: 17–67years). Male:Female ratio=1:1. The demographic data of the patients are given in Table 2. 43.3% of the patients had poor performance status (KPS<70, n=13). 86.7 % of the patients had completed the full 60 Gy of postoperative radiotherapy (n=26). 83.3% of the patients had completed the concurrent TMZ and 66.7 % were able to complete the entire treatment protocol (including adjuvant TMZ). 33.3% of patients did not receive adjuvant chemotherapy due to disease progression, toxicity etc.

Table 2. Demographic data of the patients

Variables	Variable	No (%)
Age	≤30yrs	5 (16.7)
	31-40	5 (16.7)
	41-50	8 (26.7)
	51-60	9 (20)
	>60	3 (10)
Sex	Male	15 (50)
	Female	15 (50)
Kps	<70	13 (43.3)
	≥70	17 (56.7)
Tumor size	<4	9 (30)
	≥4	21 (70)
Histology	GBM	17 (56.7)
	Anaplastic astrocytoma	10 (33.3)
	Anaplastic oligo	3 (10)
Grade	3	13 (43.3)
	4	17 (56.7)
Surgery	Biopsy only	10 (33.3)
	Partial excision	2 (6.7)
	Subtotal resection	7 (23.3)
	Near total resection	10 (33.3)
	Radical excision	1 (3.3)
RT	<60Gy	4 (13.3)
	≥60gy	26 (86.7)
Concurrent chemo	Yes	5 (16.7)
	No	25 (83.3)
Adjuvant chemo	<60	10 (33.3)
	≥60	20 (66.7)

Toxicity assessment

All patients were evaluated for toxicities during concurrent chemoradiation and adjuvant chemotherapy with TMZ. Toxicities were assessed and graded according to CTCAE version 4.0 developed by national cancer institute. Hematological toxicities include thrombocytopenia, anaemia, neutropenia and the non hematological toxicities include nausea, vomiting, headache, skin rashes, pruritis. Patients in the combined modality group were able to complete the 6 cycles of adjuvant TMZ. Majority of the hematological & non hematological toxicities were grade 1& 2. 52% of the study group had non hematological side effects and 28% had hematological side effects. Non hematological toxicities like nausea and vomiting were managed by antiemetics and dopamine receptor antagonists. Treatment was generally well tolerated with 6.7% of patients developing grade 1&2 anaemia, 16.7% of patients with grade 1&2 neutropenia (n=5) and 16.7% of patients(n=5) with grade 1&2 thrombocytopenia during the treatment. Concurrent TMZ was discontinued in two patients (6.6%) due to grade 3 myelosuppression and one patient (3.3%) developed grade thrombocytopenia. No grade 4 hematological toxicities were observed in the study group. Hematological toxicities were managed with delay or discontinuation of temozolamide therapy that was decided by the treating physician. The toxicity profile of the study group was given in Table 3.

Table 3. Toxicity profile

Toxicities	Variable	Grade 1&2 No (%)	Grade 3 No (%)
Hematological	Anemia	2 (6.7)	
	Neutropenia	5 (16.7)	2 (6.6)
	Thrombocytopenia	5 (16.7)	1 (3.3)
Non Hematological	Nausea	15 (50)	
	Vomiting	7 (23.3)	
	Headache	4 (13.3)	
	Constipation	10 (33.3)	
	Skin rash	1 (3.3)	

Discussion

Postoperative radiotherapy with concurrent TMZ followed by adjuvant chemotherapy after safe maximal surgery is the standard of care in high grade gliomas. The feasibility and safety of TMZ along with radiotherapy is higher when compared with nitrosoureas. TMZ also has radio sensitizing properties that have proved in vivo and in vitro studies.[11,12] The standard schedule of TMZ in high grade glioma patients is 200mg/m^2 for 5 days every 28days.[13-16]

In this retrospective study only 9% of the patients had grade 3 haematological toxicity. These values are comparable with the earlier study by Stupp et al. in which haematological grade 3& 4 toxicities were noticed in 7% of the patients, mainly neutropenia and thrombocytopenia.[17]

Another study found a myelosuppression in 8.7% of their patients. Leucopenia grade 3 and 4 were noticed in

3.5% and thrombopenia grade 3 and 4 in 5.2%.[18] Many retrospective studies analyzed the temozolamide toxicities and found that the frequency of grade 3 & 4 myelosuppression at a rate of 3% to 15% and grade 3 & 4 thrombocytopenia at 0–15%.[19-21] Majority of toxicities in our study were grade 1&2 and were tolerable to our patients. Gastrointestinal disturbances such as nausea and vomiting were exceedingly common. Previous studies showed that these are known as two of the most important serious side effects which affects the quality of life of the cancer patients during chemotherapy.[22]

The main hematological side effect of our study was myelosuppression, which was reversible. Most of the patients in our study were able to complete the treatment. The awareness of toxicities and evidence-based interventions for managing toxicities are important to maintain the quality of cancer care in glioma patients. The concurrent administration of radiotherapy and TMZ was feasible and well tolerated with few hematological and non-hematological toxicities. The compliance of the adjuvant therapy was satisfactory and was comparable to the previous studies. The grade 3&4 non hematological toxicities were nil in the study group. Hematological toxicities commonly occurred during concurrent chemoradiation and non haematological toxicities were common during adjuvant chemotherapy cycles.

In summary, the results of our study suggest that concomitant chemoRT with TMZ followed by six cycles of adjuvant TMZ was safe and well tolerated, and patients were able to sustain therapy. The recently published international EORTC phase III trial has demonstrated a similar benefit. Patients received Temozolomide 75 mg/m^2 everyday with radiotherapy as recommended by the EORTC/NCIC trial.

Limitation of this retrospective study is the small sample size (n=30). The demographic data & few prognostic variables of the current study could be correlated with previous studies. We have found that the compliance of the patients to radiotherapy and chemotherapy is good.

Conclusion

The compliance of temozolamide in high grade gliomas is high with less treatment interruptions and the toxicities are minimal and manageable with good outcomes, making it a good feasible protocol for high grade gliomas.

Declarations

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Author contributions

Conceptualization, V.A.R. and S.J.; Methodology, V.A.R., S.J. and K.R.S.; Formal Analysis, K.R.S.; Investigation, X.X.; Resources, V.A.R. and S.J.; Data Curation, V.A.R. and S.J.; Writing – Original Draft Preparation, V.A.R. and S.J.; Writing – Review & Editing, V.A.R., S.J. and K.R.S.

Conflicts of interest

The authors have no conflict of interest.

Data availability

The datasets used and/or analyzed during the current study are open from the corresponding author on reasonable request.

Ethics approval

Ethical approval was obtained from the Institutional ethical committee, Government Stanley Medical College and hospital (ECR/131/Inst/TN/2020/RR-21).

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