Original Article

Feasibility of preirradiation temozolomide in cases of high-grade gliomas: Our experience and review of literature

ABSTRACT

Aim: The purpose of this study was to evaluate the efficacy and safety of preradiation temozolomide (TMZ) in high-grade gliomas.

Study and Design: It is a single-center, single arm, prospective study. The study included postoperative, histopatholgically proven cases of high-grade gliomas.

Materials and Methods: Nine patients of anaplastic astrocytoma (AA) and twenty patients of glioblastoma multiforme (GBM) were enrolled in the study. All patients had undergone partial or complete resection. Three weeks after surgery, patients were started on chemotherapy, consisting of two cycles of TMZ, 150 mg/m^2/day for 5 days, repeated at an interval of 4 weeks. Patients were subsequently treated with concomitant chemoradiotherapy. A dose of 60 Gy was given over thirty fractions along with TMZ, 75 mg/m^2/day. Four cycles of TMZ were given after completion of radiotherapy, in a dose and manner similar to preradiotherapy.

Statistical Analysis and Result: Treatment-related toxicity was assessed using common terminology for toxicity criteria (CTCAE v4). Progression-free survival and overall survival (OS) analysis was done. Nearly 79% of patients completed the two cycles of preradiation chemotherapy. Chemotherapy was tolerated well. Median time to progression was 11 months and 8.2 months in AA and GBM patients, respectively. Median OS was 17.4 months in AA patients and 11.4 months in GBM patients.

Conclusions: Most patients of postoperative high-grade gliomas tolerated two cycles of TMZ. A good safety profile of TMZ allows it to be used in frontline settings, especially in high volume centers where a delay in starting radiotherapy frequently occurs. The use of TMZ before radiotherapy is a safe and feasible approach, and further studies are required to validate this approach.

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INTRODUCTION

The current standard of care for high-grade gliomas (HGG) patients is maximal safe resection followed by chemoradiation with concurrent and adjuvant temozolomide (TMZ). Despite multiple studies, the outcome remains dismal in HGG. There have been some studies regarding optimal timing between surgery and chemoradiation.[1] The patients of HGGs in Indian context generally have a poorer general condition during presentation, then undergo a major central nervous system surgery, which further deteriorates their general condition. This leads to delay in adjuvant treatment delivery while waiting for the general condition to improve. The postoperative edema takes time to settle, so the radiotherapy planning and execution may not be possible in recommended optimal time. Furthermore, the postoperative scalp edema after settlement causes loosening of the immobilization devices, resulting in inaccuracy in treatment delivery. This may require re-planning the treatment which is not feasible in high-volume centers. As a standard of care, after concurrent chemoradiation with TMZ, the patient is given six cycles of adjuvant TMZ of 5 days at an interval of 4 weeks. We hypothesize that two cycles of adjuvant TMZ can be given before the start of radiotherapy so that patient can be given optimal treatment in timely manner without a gap in treatment. A very few similar studies have been done in Western population. We intend to assess the feasibility of this approach, progression-free survival (PFS), and

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overall survival (OS). Other similar studies were explored, and the data were compiled.

MATERIALS AND METHODS

Study design

The study is designed as a single arm, single-center, prospective study. The study included only newly diagnosed, and histopatholgically proven patients of high-grade (WHO Grade III and IV) gliomas who had undergone partial or complete resection. The study was approved by ethics committee of the department.

Eligibility criteria

A total of 29 patients of HGG registered in the radiotherapy department of our institute were included in this study after analysis of eligibility criteria and an informed consent.

Patients of age more than 18 years, of either sex with adequate baseline investigations, were recruited in the study. This included serum hemoglobin >10 gm%, adequate total leukocyte count, platelet Count >1,00,000/cu. mm, absolute neutrophil count >1500/cu. mm, bilirubin <2 mg/dl, SGOT <50 IU, SGPT <50 IU, ALP < 280 IU, blood urea <50 mg/dl, serum creatinine <2 mg/dl, and glomerular filtration rate >50 ml/min. An magnetic resonance imaging (MRI) scan was obtained within 72 h postresection.

Patients with performance status ECOG 4 or with immunocompromised status such as HIV seropositivity, organ transplant recipients, congenital immunodeficiency syndromes, or any other condition causing immunological compromise were excluded. Patients having a history of any prior oncologic treatment with other chemotherapy or radiotherapy or having any comorbidity which compromises chemoradiotherapy treatment schedules, for example, cardiorespiratory disease, renal disease, or uncontrolled diabetes mellitus were also excluded.

Treatment protocol

After baseline investigations, a complete physical and neurological examination was done in all patients at the time of recruitment in the study. A baseline contrast-enhanced MRI or computed tomography (CT) scan was also done.

Pre-irradiation chemotherapy

Tab TMZ 150 mg/m^2 D1-D5, two such cycles at an interval of 4 weeks were given. Radiotherapy was started 4 weeks after last cycle of TMZ chemotherapy.

External beam radiotherapy

A total of 60 Gray/30 fractions using Co^{60} γ with daily concurrent TMZ 75 mg/m^2 was planned.

Adjuvant chemotherapy

After completion of radiation therapy (RT), further four more cycles of adjuvant TMZ 150 mg/m^2 D1-D5 at an interval of 4 weeks were prescribed so that total number of cycles of TMZ are 6.

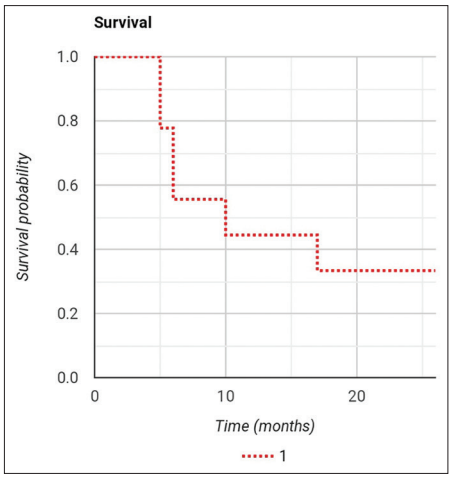

Figure 1: Kaplan–Meier curve for progression-free survival of anaplastic astrocytoma patients

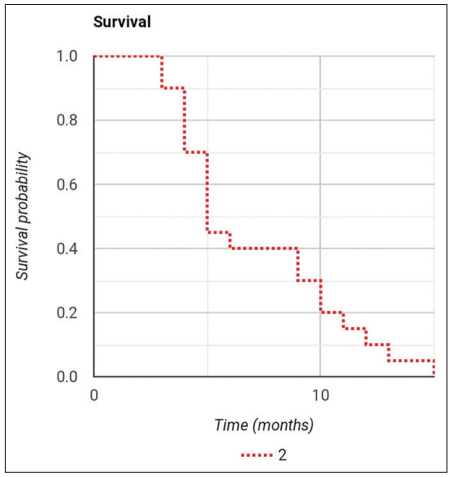

Figure 2: Kaplan–Meier curve for progression-free survival of glioblastoma multiforme patients

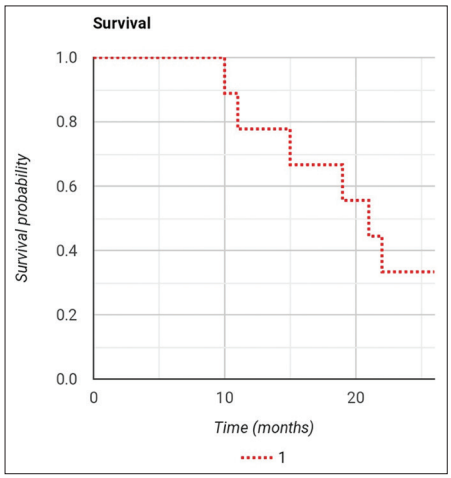

Figure 3: Kaplan–Meier curve for overall survival of anaplastic astrocytoma patients

Hematologic analysis was performed at the beginning of each cycle and within 3 weeks of first dose of TMZ.

Evaluation of treatment response

Patients were followed up every 3 months for 2 years with a contrast MRI or CT scan and a detailed neurological examination.

The feasibility and safety of pre irradiation TMZ and subsequent concomitant chemoradiotherapy in HGG were assessed. Patients were followed up every 3 months for 2 years with a contrast MRI or CT scan & a detailed neurological examination. PFS & OS were recorded.

Primary end point

Treatment related acute toxicity assessment was done using Common Terminology Criteria for Adverse Events version 4 (CTCAE v4 developed by National Cancer Institute, USA) for chemotherapy induced toxicity. Radiotherapy induced toxicity assessment was done by RTOG criteria.

Secondary endpoint

PFS, which is defined as date of recruitment in the study to the date of first reported clinical or radiological disease PFS and OS, defined as the duration of time from date of diagnosis to the date of death or last follow-up.

Observations

The demographic data and baseline disease characteristics are outlined in Table 1. A total of 29 patients with a diagnosis of either anaplastic astrocytoma (AA) ($n = 9$) or glioblastoma multiforme (GBM) ($n = 20$) were enrolled in the study. The median age of patients of AA and of GBM was 38.5 years and 49.9 years, respectively. There was male preponderance in both the groups. Most of the patients enrolled in study had ECOG score of 1 or 2, before starting TMZ. One (11.1%) of patients of AA and three (15%) patients of GBM underwent complete resection, while the rest of the patients in both the groups underwent subtotal resection.

The median time to start first cycle of TMZ in both groups of patients was 28 days. The second cycle was started after 4 weeks of first cycle. Overall compliance of 79% was observed in the entire cohort for two cycles of preradiotherapy TMZ. Out of nine patients of AA, 8 (88%) patients completed the assigned treatment of two cycles. The number was lower in GBM group (77.7%). Out of these, total seven patients who failed to complete two cycles of preradiation TMZ, six patients had disease progression and discontinued the treatment. One patient failed to complete the planned treatment because of socioeconomic constraints. TMZ-induced toxicity was not a reported cause to discontinue the treatment in any of the patient enrolled for treatment. No death was reported during this phase of protocol. Treatment completion and causes of discontinuation are summarized in Tables 2 and 3.

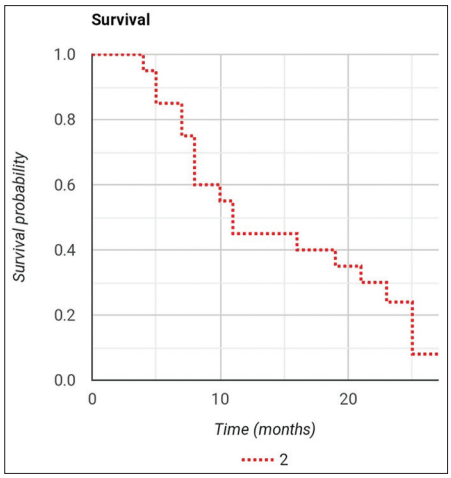

Figure 4: Kaplan–Meier curve for overall survival of glioblastoma multiforme patients

Table 1: Patient and tumour characteristics

	Anaplastic astrocytoma (*n*=9), *n* (%)	Glioblastoma multiforme (*n*=20), *n* (%)
Median age (years), range	38.5 (26-59)	49.9 (22-68)
Sex		
Male	8 (91.6)	11 (55)
Female	1 (8.4)	9 (45)
Surgery		
complete resection	1 (11.1)	3 (15)
Subtotal resection	8 (88.8)	17 (85)
ECOG 1	6 (66.6)	10 (50)
2	2 (22.2)	8 (40)
3	1 (11.1)	2 (10)
Prior treatment	Nil	Nil

Table 2: Treatment with temozolomide (preirradiation)

	Anaplastic astrocytoma (*n*=9), *n* (%)	GBM (*n*=20), *n* (%)
Enrolled	9	20
Median time to initiate first cycle (days)	28	28
Completed 1 cycle	9 (100)	18 (90.0)
Completed 2 cycles	8 (88.8)	14 (70.0)

Table 3: Causes of failure of completion of assigned treatment (preirradiation temozolomide)

Cause	Number of patients	Percentage of total patients in the study
Disease progression	6	20.6
Unacceptable toxicity	0	Nil
Noncompliance	1	3.4
Death	0	Nil

On radiological assessment, out of total 22 analyzable patients at the end of completion of two cycles, two patients, one from each group had complete remission at the end of chemotherapy, three had progressive disease, while the rest had stable disease.

In the CTCAE, a score of 1 indicates mild adverse effects, a score of 2 moderate adverse effects, a score 3 severe adverse effects, and a score of 4 life-threatening adverse effects. Hematologic toxicities, including thrombocytopenia, neutropenia, leukopenia, and anemia, were assessed. Among nonhematologic toxicities, anorexia, nausea, vomiting, constipation, diarrhea, fatigue, pruritus/itching, skin rash, fever, and infection were assessed.

TMZ is a safe and well-tolerated drug. Both the cycles were administered at full doses in 76% of the patients. The adverse events are tabulated in Table 4. The main adverse event reported was myelosuppression. Only one patient developed Grade 3 neutropenia after the completion of second cycle of chemotherapy. Grade 4 hematologic toxicity was nil with the two cycles of TMZ. Out of all hematologic toxicities reported, it was observed that majority were Grade 1 and Grade 2 leukopoenia and neutropenia (cumulative incidence 24.1% and 20.6%) in both the groups followed closely (17.2%) by thrombocytopenia. The most common nonhematologic adverse effect reported was fatigue (37.9%). Total nine patients suffered with nausea (31.3%) and 27.5% complained constipation. None of the patient presented with infection. Some other adverse events such as ataxia, convulsions, speech difficulties, and behavioral problems were reported which were unrelated to TMZ. The adverse events did not require any dose reduction or hospitalization. There was no delay in subsequent treatment with definitive concomitant chemoradiotherapy.

A total of 22 patients were recruited for definitive treatment with radiotherapy and concomitant TMZ after completing two cycles of pre-RT TMZ. Thirteen patients out of this entire group of 22, i.e., 58%, completed the planned treatment of concomitant chemoradiotherapy. The rest of the patients discontinued the treatment either because of poor clinical status or withdrawal of consent from protocol.

Duration of radiotherapy in both groups ranged between 13 and 52 days.

Most of the documented toxicities of the combined modality approach were mild-to-moderate grade. Of radiotherapy-induced toxicity, Grade 1 external otitis media were reported in two patients, and dermatitis of Grade 1 was reported in four patients.

Seven (all from GBM) patients died before completing the scheduled adjuvant treatment because of disease progression. Chemotherapy-induced Grade 3 leukopoenia was observed in a total 8% of cases of both the groups. A small number of patients had gastrointestinal complaints including nausea and vomiting.

PFS was 11 months and 8.2 months in AA and glioblastoma groups, respectively [Table 5]. Median OS was 17.4 months in AA group, whereas it was 11.4 months in glioblastoma (Ref: Figures 1-4. Kaplan–Meier survival curve for PFS and OS).

DISCUSSION

HGGs are usually fatal. Despite multimodality treatments, the outcome of patients of these tumors remains poor. Standard therapy consists of surgical resection to the extent that is safely feasible, followed by adjuvant radiotherapy and chemotherapy.

Various chemotherapeutic agents including cisplatin, lomustine, and vincristine have been used for the treatment of HGGs. Since 2005, TMZ has become a standard regimen in the treatment of malignant gliomas. TMZ is an orally administered, second-generation alkylating chemotherapeutic drug that methylates DNA in a way that prevents tumor cell proliferation. It is quickly and almost completely absorbed from the gut and readily penetrates the blood–brain barrier,

Table 4: Adverse effects with pre irradiation temozolomide

Adverse events	Grade I, *n* (%)	Grade II, *n* (%)	Grade III, *n* (%)	Grade IV, *n* (%)	Total (*n*=29), *n* (%)
Hematologic					
Leukopenia	4 (13.7)	3 (10.3)	0	0	7 (24)
Neutropenia	3 (10.3)	3 (10.3)	1 (3.4)	0	7 (24)
Thrombocytopenia	4 (13.7)	1 (3.4)	0	0	5 (17.2)
Anemia	2 (6.8)	2 (6.8)	0	0	4 (13.7)
Nonhematologic					
Nausea	5 (17.2)	4 (13.7)	0	0	9 (31)
Vomiting	3 (10.3)	3 (10.3)	0	0	6 (20.6)
Anorexia	2 (6.8)	5 (17.2)	0	0	7 (24)
Constipation	5 (17.2)	3 (10.3)	0	0	8 (27.5)
Diarrhea	1 (3.4)	3 (10.3)	0	0	4 (13.7)
Fatigue	6 (20.6)	5 (17.2)	0	0	11 (37.9)
Fever	2 (6.8)	3 (10.3)	0	0	5 (17.2)
Headache	4 (13.7)	5 (17.2)	0	0	9 (31)
Allergic reactions					
Itching/skin rash	2 (6.8)	3 (10.3)	0		5 (17.2)
Infections	0	0	0		

*Toxicities were assessed by using the CTCAE version 4.0 developed by the national cancer institute, Percentages represent toxicities documented over 2 cycles received. CTCAE=Common terminology criteria for adverse events

Table 5: Overall and progression-free survival according to treatment group

Variable	Number of patients (*n*=9)	*n*=20
Median overall survival (months)	17.4	11.4
OS, *n* (%)		
At 6 months	9 (100)	13 (63)
At 12 months	7 (78)	5 (26)
At 18 months	6 (67)	4 (22.2)
At 24 months	3 (33.3)	3 (14.8)
Median progression-free survival (months)	11	8.2
Progression-free survival, *n* (%)		
At 6 months	5 (55.5)	8 (40.0)
At 12 months	4 (44.4)	2 (10)
At 18 months	3 (33.3)	0
At 24 months	2 (22.2)	0

OS: Overall survival

the concentration in the cerebrospinal fluid is 30% of the concentration in the blood. It has a good safety profile.

A phase-III trial by Gilbert MR[2] compared standard adjuvant TMZ with dose-dense schedule in newly diagnosed glioblastoma to determine if intensified TMZ improves overall survival. This study did not demonstrate any statistical difference in the overall survival with dose-dense TMZ.

The current trial was designed to give two cycles of adjuvant TMZ before the start of radiotherapy so that patient can be given optimal treatment in timely manner without a gap in definitive treatment. Cytotoxic drugs may be more effective if given before radiotherapy as response can be assessed independent of effects of radiation.[3] There is also a rationale for administering chemotherapeutic agent before radiotherapy to allow the maximum distribution of the agents that may otherwise be compromised due to alteration of blood vessels by radiotherapy.

The optimal time to start chemoradiotherapy in postoperative cases of high-grade glioma has been a point of debate. Few studies have found a significantly increase survival if the time to initiation of radiotherapy is prolonged. This may be explained by a better healing and a full recovery from surgery. Hence, delaying radiotherapy may not adversely affect the outcome in this group of patients. Many other approaches are emerging to improve the prospects of patients of HGG. Nanostructured lipid carriers for better delivery of TMZ in brain parenchyma has shown promising result is in preclinical phase. The role of tumor treating fields (TTF), an antimitotic treatment delivered through alternating electric fields is being researched along with chemotherapy and radiotherapy. It has a synergistic role as it delays the repair of DNA damage caused by radiotherapy and chemotherapy.

Our experience with preradiation chemotherapy is comparable to other studies published so far. It was observed that, at 6 months, PFS was better in AA group. The median time to progress was 11 months and 8.2 months in AA group and GBM patients, respectively. The median OS for both the AA and GBM groups is 17.4 months and 8.4 months respectively. OS rate at 2 years was 33.3% in AA group and 14.8% in GBM group. The results observed in our study are comparable to other studies done with the similar intent.

Many investigators have used combination chemotherapy in HGG. A combination of cisplatin and BCNU was given by Gilbert *et al*. Although 22% patients of patients responded, but the regimen was associated with a significant hematologic toxicity. The adverse effects reported in our study with single drug, i. e., TMZ are mostly mild to moderate, predominantly hematologic. The adverse events did not require any dose reduction or hospitalization and there was no delay in subsequent treatment with definitive concomitant chemoradiotherapy.

The neoadjuvant strategy with TMZ used in the current study seems to be a safe and promising approach.

Many other approaches are emerging to improve the prospects of patients of HGG. Nanostructured lipid carriers for better delivery of TMZ in brain parenchyma have shown promising result is in preclinical phase.[4] The role of TTF, an antimitotic treatment delivered through alternating electric fields is being researched along with chemotherapy and radiotherapy. It has a synergistic role as it delays the repair of DNA damage caused by radiotherapy and chemotherapy.[5]

REVIEW OF LITERATURE

The standard of care in GBM was established after famous phase III trial by Stupp *et al*.[6] Five hundred and seventy-three patients of age 18–70 were randomized to radiotherapy alone to a dose of 60 Gy/30 fractions/6 weeks versus concurrent chemoradiation to a dose of 60 Gy/30 fractions over 6 weeks with daily TMZ (75 mg/m^2/day) 7 days/week followed by adjuvant TMZ (150–200 mg/m^2/day for 5 days) at an interval of 4 weeks for 6 months. The primary end point was OS. After a median follow-up of 28 months, the concurrent and adjuvant TMZ significantly improved median survival (12.1 vs. 14.6 months, $P < 0.001$). The 2-year survival rates were 26% and 6% with and without TMZ, respectively.

There are many studies showing benefit of adjuvant TMZ in HGG. Most of them are in concurrent and adjuvant setting after the completion of postoperative chemoradiotherapy. There have been some studies with different chemotherapy regimens before RT in pre-TMZ era. We searched the resources available on internet. Preirradiation studies were compiled, and the results were compared [Table 6].

Recht *et al.*[7] treated thirty patients of malignant supratentorial gliomas with preirradiation chemotherapy protocol consisting of two courses of intracarotid cisplatin, 90 mg/m^2 followed by intravenous BCNU, 200 mg/m^2. Eighty-three percent patients completed the entire protocol with median time to disease PFS and OS of 53 weeks and 61 weeks, respectively.

Table 6: Studies of preradiotherapy chemotherapy in gliomas

Author	Year of publication	*n*	Pre RT-chemo-regimen	Response rate	PFS	OS	Remarks
Recht *et al*.[7]	1990	30	2 cycles of (intracarotid cisplatin → BCNU)	13%-decreased by≥50%, 4% increased in size	12 months	14 months	Malignant supratentorial gliomas
Dropcho *et al*.[8]	1992	26	4 cycles intracarotid CDDP	10 (45%) ≥25% decrease, 3 (14%) ≥70% decrease in tumour area	NR	NR	Anaplastic astrocytoma and glioblastoma multiforme
Kirby *et al*.[9]	1996	37	Procarbazine. lomutine and vincristine or lomustine alone	Any response after 1st cycle - 5, PD - 7	26 weeks	60 weeks	Glioblastomas, anaplastic astrocytoma and anaplastic mixed gliomas
Jeremic *et al*.[10]	1999	45	2 cycles carboplatin and etoposide	PR - 7 SD - 19 PD - 3	12 months	14 months	Anaplastic astrocytomas
Dazzi *et al*.[11]	2000	18	BCNU and cisplatin	CR=3, PR=4, RR=54%	NR	9 months	Glioblastoma multiforme
Gilbert *et al*.[12]	2000	47	3 cycles of BCNU and CDDP	1 - CR 10 - PR 18 - SD	NR	9 months	Glioblastoma multiforme
Gilbert *et al*.[13]	2002	57	Max 4 cycles TMZ 200 mg/m2 D1-5, at an interval of 4 weeks	22 - ORR, 6 - PR, 18 - SD	AA - 7.3 months, GGM - 3.9 months	AA - 23.5 months, GBM - 13.2 months	GBM and AA
Chang *et al*.[14]	2004	41	4 cycles TMZ and BCNU	2% CR, 27% PR 54% SD 17% PD	NR	NR	AA and AODG only
Barrie *et al*.[15]	2005	40	4 cycles BCNU and TMZ	ORR - 42.5%, CR - 2, PR - 15	7.4 months	12.7 months	Inoperable GBM only
Vogelbaum *et al*.[16]	2015	40	6 cycles TMZ 150 mg/m^2/day on days 1–7 and days 15–21 of a 28-day cycle (7-day on/7-day off)		5.8 years	NR	AO and MOA only

PFS: Progression-free survival, OS: Overall survival, AA: Anaplastic astrocytoma, GBM: Glioblastoma multiforme, CDDP: Cisplatin, BCNU: 1, 3 bis (2-chlorethyl)-1-nitrosurea, TMZ: Temozolomide, SD: Stable disea5se, CR: Complete response, PR: Partial response, NR: Not reported, ORR: Objective response rate, RR: Response rate, PD: Progressive disease, AODG: Anaplastic oligodendroglioma, AO: Anaplastic oligodendroglioma, MOA: Mixed anaplastic oligoastrocytoma, RT: Radiotherapy

In a trial by Kirby *et al*.,[9] 37 newly diagnosed cases of glioblastoma, AA, and anaplastic mixed gliomas were treated with one cycle of procarbazine, lomustine, and vincristine or lomustine alone, before radiotherapy. They concluded that 16% of patients of GBM had partial response to first cycle of chemotherapy. For the entire group, the median time to progression was 26 weeks and the median survival of 60 weeks. Preirradiation carboplatin and etoposide and accelerated hyperfractionated RT were given in a phase II trial by Jeremic *et al.*[10] in cases of high-grade astrocytomas. Toxicities of this combined modality approach were mild to moderate while OS was 14 months.

Intravenous infusion of BCNU and cisplatinum for 72 h up to 3 monthly cycles followed by radiotherapy in newly diagnosed cases of GBM was given in a phase II trial by Dazzi *et al*. Overall, 79% of patients were able to complete at least two cycles of treatment. Around 48% of patients experienced Grade 4 toxicity.

In a phase II study by Gilbert *et al*., 57 patients (51 adult and 6 pediatric) with newly diagnosed supratentorial GBM or AA were treated with TMZ (200 mg/m^2/day for 5 consecutive days every 28 days) for a maximum of four cycles. All patients were then treated with external beam radiotherapy. Among adult patients with AA, the median PFS and OS rates were 7.6 and 23.5 months, respectively. The median PFS and OS rates among adult patients with GBM were 3.9 and 13.2 months, respectively, which is similar to that of postirradiation adjuvant TMZ trials. Grades 3 and 4 adverse events were reported in 16 (28%) and 7 (12%) patients, respectively. They concluded that TMZ was safe and effective in treating newly diagnosed GBM and AA before radiotherapy.[2]

In a study on patients of GBM, Barrié *et al*. concluded that TMZ and BCNU as neoadjuvant therapy in inoperable cases exhibited promising activity with a good safety profile. Sixty percent of the patients completed 4 cycles of BCNU and TMZ. Two patients out of a cohort of 37 patients had complete response and 15 had partial response. No patient discontinued therapy because of toxicity. PFS was 7.4 months and OS was 12.7 months.

Chang *et al*. in their work published on 2004 gave TMZ along with BCNU to estimate toxicity and efficacy of this combination regimen in newly diagnosed anaplastic gliomas. Nearly 59%

of patients completed 4 cycles of chemotherapy. Around did not complete chemotherapy because of toxicity, while 46% of patients experienced Grade 3 or 4 thrombocytopenia.

Long-term results of Phase II study of preradiation chemotherapy in 48 patients of AA and mixed anaplastic oligo astrocytoma having 1p/19q codeletion with 6 cycles of TMZ, 150 mg/m^2 Day 1–7 and 15–21 of 28 days cycle, were published in 2015. Michael A. Vogelbaum *et al*.[16] reported an impressive median PFS of 5.8 years. There is a paucity of data in literature after this trial.

CONCLUSIONS

Most patients of postoperative high-grade gliomas tolerated two cycles of TMZ. A good safety profile of TMZ allows it to be used in front line settings, especially in high volume centers where a delay in starting radiotherapy frequently occurs. The use of TMZ before radiotherapy is a safe and feasible approach and further studies are required to validate this approach.

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Conflicts of interest
There are no conflicts of interest.

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