ORIGINAL ARTICLE

When Temozolomide Alone Fails: Adding Procarbazine in Salvage Therapy of Glioma

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ABSTRACT: ***Background:*** Since temozolomide (TMZ) entry into routine practice in the first-line management of glial tumors, post-TMZ recurrences present a growing challenge. Without standard chemotherapy for TMZ failure, care in such palliative settings requires consideration not only of efficacy but of toxicity and convenience. ***Methods:*** At our institution, a combination regimen has been used: oral alkylating agents procarbazine (PCB) (100-150 mg/m^2/day) and TMZ (150-200 mg/m^2/day) administered on days 1-5 of a 28-day cycle. This treatment has been initiated upon radiological and/or clinical disease progression, and continued until evidence of further progression or toxicity. We retrospectively reviewed our experence with this regimen. ***Results:*** Since November 2004, 17 patients (median age 53) were treated for histologically confirmed glioma (glioblastoma multiforme (GBM), N=12; Grade 3 glioma, N=3; Grade 2 glioma, N=2) after a median of 2 recurrences. TMZ was previously given either as adjuvant therapy (post-chemoradiotherapy maintenance in 8 of 13 cases) or as salvage monotherapy (4 cases). Of 16 evaluable cases, 14 (13 high grade tumors) showed O-6-methylguanine-DNA methyltransferase (MGMT) promoter methylation. Two patients achieved partial response and one had complete response by RECIST criteria. Disease progressed after a median of 4 cycles (range 1 to 11+), with an actuarial progression-free survival of 42% after 6 cycles. Grade 3/4 toxicity was rare, and no dose reductions were needed. One patient discontinued treatment due to procarbazine hypersensitivity. ***Conclusion:*** Combination PCB-TMZ is well-tolerated, with modest activity in TMZ-exposed glioma.

RÉSUMÉ: Échec du témozolomide seul : ajout de la procarbazine comme agent de rattrapage dans le traitement du gliome. ***Contexte :*** Depuis que le témozolomide (TMZ) est utilisé de routine comme traitement majeur des tumeurs gliales, les rechutes après le traitement par le TMZ présentent un défi de plus en plus grand. Quand on fait face à un échec du traitement par le TMZ et en l'absence de chimiothérapie standard, on doit considérer non seulement l'efficacité mais aussi la toxicité et les aspects pratiques du traitement dans ce contexte palliatif. ***Méthodes :*** Dans notre institution, nous avons utilisé un traitement d'association : deux agents alkylants oraux, la procarbazine (PCB) (100-150 mg/m2/ j) et le TMZ (150-200 mg/m2/ j), administrés aux jours 1-5 d'un cycle de 28 jours. Ce traitement était commencé lorsqu'on observait une progression radiologique et/ou clinique de la tumeur et il était maintenu jusqu'à ce qu'on observe une progression plus marquée ou de la toxicité. Nous avons fait une revue rétrospective de ce mode de traitement. ***Résultats :*** Depuis novembre 2004, 17 patients dont l'âge médian était de 53 ans ont été traités pour un gliome confirmé par l'histologie (glioblastome muliforme (GBM) N = 12; gliome de grade 3, N = 3; gliome de grade 2, N = 2) après un nombre de rechutes médian de 2. Le TMZ avait été donné antérieurement soit comme traitement adjuvant (traitement d'entretien post-chimioradiothérapie chez 8 patients sur 13) ou en monothérapie comme traitement de rattrapage (chez 4 patients). Chez 14 (13 cas de tumeurs de haut grade) des 16 patients évaluables, on a observé une méthylation du promoteur de l'O-6-méthylguanine-DNA méthyltransférase (MGMT). Deux patients ont eu une réponse partielle et un a eu une réponse complète selon les critères RECIST. La maladie a progressé après 1 à 11 cycles ou plus, médiane de 4 cycles, avec une survie actuarielle sans progression de 42% après 6 cycles. Une toxicité de grade 3/4 était rare et aucune réduction de dose n'a été nécessaire. Un patient a cessé le traitement à cause d'une hypersensibilité à la procarbazine. ***Conclusion :*** La combinaison PCB-TMZ est bien tolérée et son efficacité sur les gliomes qui ont déjà été exposés au TMZ est modeste.

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Glioma treatment practices have been profoundly altered in recent years with the demonstration that temozolomide (TMZ) improves survival when added to external beam radiotherapy (EBRT) for newly diagnosed glioblastoma multiforme (GBM).[1] Where use of TMZ was previously limited to relapses of malignant glioma, it is now first-line therapy. As these TMZ-treated tumors progress or recur, we face the emerging entity of post-TMZ failure.

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Although there exists extensive literature on the chemotherapy of recurrent glioma, including recent randomized trials of novel combinations or targeted therapies, the populations studied vary widely in their prior chemotherapy experience. No randomized data exists to guide therapy for those gliomas specifically failing TMZ. In a phase II setting, the combination of irinotecan and carmustine resulted in a partial response (PR) rate of 21.4% and a six-month progression-free survival (PFS) of 30.3% for GBM recurring or progressing after TMZ.[2]

Purported mechanisms of resistance to TMZ, whether inherent or acquired, involve the repair of potentially lethal DNA damage. This repair is mediated by the ubiquitous enzyme O^6-alkylguanine-alkyltransferase, also known as O^6-methylguanine-DNA methyltransferase (MGMT). Several strategies have been attempted to overcome resistance through MGMT depletion. These include alternative substrate binding, as with the non-cytotoxic O^6-benzylguanine,[3] sustained low-dose TMZ[4-7] and shorter cycles of higher dose TMZ.[8] In two extreme examples, unintended overdose of TMZ (200 mg/m^2/day for five days/week for six weeks; 2835 mg/m^2/day for two days) resulted in a lasting PR of at least 2.5 years for a recurrent anaplastic astrocytoma and a 22-month PFS for a newly diagnosed GBM.[9,10]

Following an interval of disease stability, responses can be seen to TMZ re-challenge. In one retrospective review, TMZ was re-administered (150-200 mg/m^2/day for five days, every 28 days) to 14 patients with recurrent or progressive glioma. All were known to have responded to TMZ in the past. Two complete responses (CR) were achieved, with an overall response of 43%, and no significant toxicity. The median time to progression was three months and the six-month progression-free survival was 36%.[11] This is in keeping with phase II results for novel chemotherapy combinations or targeted therapies for recurrent malignant gliomas, where six-month PFS ranged from 0% to 48%.[2,12,13]

Materials and Methods

At our institution, a combination regimen of oral alkylating agents has been offered to patients at the time of radiological recurrence or progression of glioma, if: (a) there was past exposure to TMZ, and (b) performance status is reasonable (karnofsky performance status ≥ 60). In this review, we present the results of our experience with this palliative regimen, and we assess the MGMT promoter methylation profiles in this tumor set.

Treatment Regimen. Oral procarbazine (PCB), at a dose of 100-150 mg/m^2/day, was administered in conjunction with TMZ, at a dose of 150-200 mg/m^2/day, on the first 5 days of a 28-day cycle. Cycles were repeated until clinical or radiographic disease progression, or until unacceptable toxicity occurred.

Assessment of Treatment Response. Patients were assessed by their treating physician at one or two month intervals. Imaging was typically obtained after every 2-3 cycles of PCB-TMZ to assess for response – more frequently if clinically indicated. Gadolinium-enhanced MRI was the preferred imaging modality, although CT scans were sometimes obtained. Response Evaluation Criteria in Solid Tumors (RECIST) guidelines were used to assess for tumor reponse.

Toxicity. All patients were monitored for toxicity. Hematological and biochemical evaluation was repeated prior to each cycle of PCB-TMZ. Treatment proceeded when neutrophil count remained above 1.0 x10^9/L, and when platelets exceeded 75 x10^9/L. Treatment was deferred for at least one week otherwise, and re-initiated when blood counts rose to acceptable levels. Toxicities were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.

MGMT Promoter Methylation. DNA was extracted from frozen or formalin-fixed paraffin embedded specimens using QIAmp DNA minikit (QUIAGEN Inc., Mississauga, ON). Surgical specimens were obtained either at the time of operable recurrence or tumor upgrading, or else at the time of initial glioma diagnosis. After denaturation with sodium hydroxide and modification by sodium bisulfite, DNA samples were purified using the Wizard DNA purification kit (Promega U.S., Madison, WI). Methylation-specific PCR was performed with primers for unmethylated and methylated alleles of MGMT according to well-described methods.[14] Primers included: 5'TTTGTGTTT TGAGTTTGTAGGTTTTTGT3' (forward) and 5'AACTCC ACACTCTTCCAAAAACAAAA CA3' (reverse) for the unmethylated reaction; and 5'TTTCGACGTTCGTAGGTT TTCGC3' (forward) and 5'GCACTCTTCCGAAAACGAA ACG3' (reverse) for the methylated reaction. Products of 90 base pairs and 80 base pairs were separated by electrophoresis using an 8% acrylamide gel. Placental DNA and Hela cell DNA were used as negative and positive controls, respectively. After staining with SYBR Green (Molecular Probes, Invitrogen Canada Inc., Burlington, ON), the gel was visualized using a Storm Fluorescence Scanner (Molecular Dynamics, GE Healthcare, Piscataway, NJ).

Statistical Analysis. Progression-free and overall survival (PFS, OS) were assessed by the Kaplan-Meier life table method using the SPSS software package (Version 14.0.0, SPSS Inc., Chicago, IL).

Results

Patient Characteristics. Seventeen patients (12 men and 5 women) received PCB-TMZ between November 2004 and May 2006. Their median age was 53 years (range 33-72). All patients had histologically confirmed glioma: 12 with GBM, 3 with anaplastic oligodendroglioma or oligoastrocytoma, and 2 with Grade 2 oligodendroglioma (Table 1).

PCB-TMZ was given for a first recurrence in eight cases. The median number of instances of glioma recurrence/progression prior to our intervention was 2 (range 1-4). All patients had previous surgical intervention, and all had had a full course of EBRT (50–60Gy). In three cases (one of which was a responder), disease recurrence prompting PCB-TMZ was diagnosed on imaging within two months of radiotherapy. Although pseudo-progression cannot be excluded, in each case a change in therapy

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Table: Patient characteristics and response to salvage PCB-TMZ

No.	Age	Sex	Histology[1]	Prior treatment	Status post PCB-TMZ
1	44	F	Oligodendroglioma, Grade 2	- Resection, then post-op RT - TMZ	DOD at 9 m
2	59	M	Oligodendroglioma, Grade 2	- Biopsy, then RT - PCV - TMZ - BCNU	AWD at 4 m
*3	33	M	Oligodendroglioma, Grade 3	- Biopsy, then post-op TMZ (1 cycle) - RT with TMZ, then maintenance (9 cycles)	ADF at 5 m[2]
4	51	M	Oligodendroglioma, Grade 3	- Partial resection, then post-op RT - Partial resection, then post-op TMZ - Radiosurgery	DOD at 10 m
5	44	F	GBM	- Resection, then post-op RT with TMZ, then maintenance (1 cycle)	AWD at 5 m
6	47	F	GBM	- Gross total resection, then post-op RT with TMZ, then maintenance (1 cycle)	DOD at 8 m
7	57	F	GBM	- Biopsy, then RT - Partial resection, then post-op TMZ	AWD at 3 m
8	64	F	GBM	- Gross total resection, then post-op RT with TMZ, then maintenance (6 cycles) - Partial resection	AWD at 4 m
9	38	M	GBM	- Partial resection - Partial resection - Partial resection, with post-op RT - Partial resection, with post-op TMZ	AWD at 4 m[3]
10	44	M	GBM	- Partial resection, then post-op RT with TMZ, then maintenance (2 cycles)	DOD at 6 m
*11	46	M	GBM	- Partial resection, then post-op RT - Partial resection, then post-op TMZ - Partial resection	AWD at 6 m[4]
12	53	M	GBM	- Resection, then post-op RT - TMZ	DOD at 4 m
*13	54	M	GBM	- Partial resection, then post-op RT with TMZ, then maintenance (2 cycles)	AWD at 11 m
14	57	M	GBM	- Partial resection, then post-op RT with gefitinib - TMZ alone	DOD at 13 m
15	59	M	GBM	- Gross total resection, then post-op RT with TMZ, then maintenance (2 cycles)	DOD at 2 m
16	68	M	GBM	- Partial resection, then post-op RT with TMZ, then maintenance (4 cycles)	DOD at 11 m
17	72	M	GBM	- Biopsy, then post-op RT with gefitinib - Gross total resection, then post-op TMZ	AWD at 1 m

[1] In patient with multiple resections, highest grade reported; [2] One cycle of TMZ was given while awaiting symptomatic improvement before initiating radiotherapy; [3] This patient was lost to follow-up; [4] PCB-TMZ was discontinued due to drug reaction; * Three patients with clinical responses to PCB-TMZ; Abbreviations: ADF, alive and disease-free; AWD, alive with disease; BCNU, carmustine; DOD, dead of disease; PCB, procarbazine; PCV, combination procarbazine-lomustine-vincristine; post-op, post-operative; RT, radiotherapy; TMZ, temozolomide.

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was felt to be necessary based on imaging and/or clinical findings. Steroid use was not recorded. Two patients, both PCB-TMZ non-responders, did undergo radiosurgery during the course of their treatment. Three patients had had prior non-TMZ systemic therapy: 2 received gefitinib, and one had both prior PCV (PCB, lomustine (CCNU), and vincristine) and carmustine (BCNU).

All patients had previous exposure to TMZ. When not given concurrently with radiation, TMZ had been administered daily for five days, in 28-day cycles. In eight cases, TMZ was first given during adjuvant radiation and then during maintenance phase (median 2 maintenance cycles; range 1-9). In five cases, TMZ had been given following surgery for glioma recurrence (median 8 cycles; range 1-16). In four cases, TMZ was given as monotherapy for unresectable glioma recurrence. For 15 of 17 patients, PCB was added to ongoing TMZ. Temozolomide dose in this context was unchanged.

Treatment Response and Survival. An overall response rate of 17.6% was seen, with one CR after 5 cycles of PCB-TMZ, and two PR. One patient was still in PR after 11 cycles (Figure 1). Disease progressed after a median of 4 cycles of PCB-TMZ (Figure 2). The PFS after six cycles was 42%. All patients receiving six cycles or more had GBM histology. Median overall survival was nine months.

Toxicity. Few Grade 3 or 4 toxicities were seen. There was one instance each of Grade 3 neutropenia and lymphopenia, without clinical consequence. One patient required parenteral support for severe nausea and vomiting after the first cycle of PCB-TMZ, only to undergo four additional cycles without any support or further adverse effect. No dose reductions were incurred. We discontinued treatment in one case due to Grade 3 hypersensitivity to PCB.

MGMT Promoter Methylation. Sixteen specimens were evaluable by methylation-specific PCR. Thirteen samples (all but one showed GBM histology) were methylated, two were unmethylated, and one exhibited both methylated and unmethylated status (GBM). Responders showed both

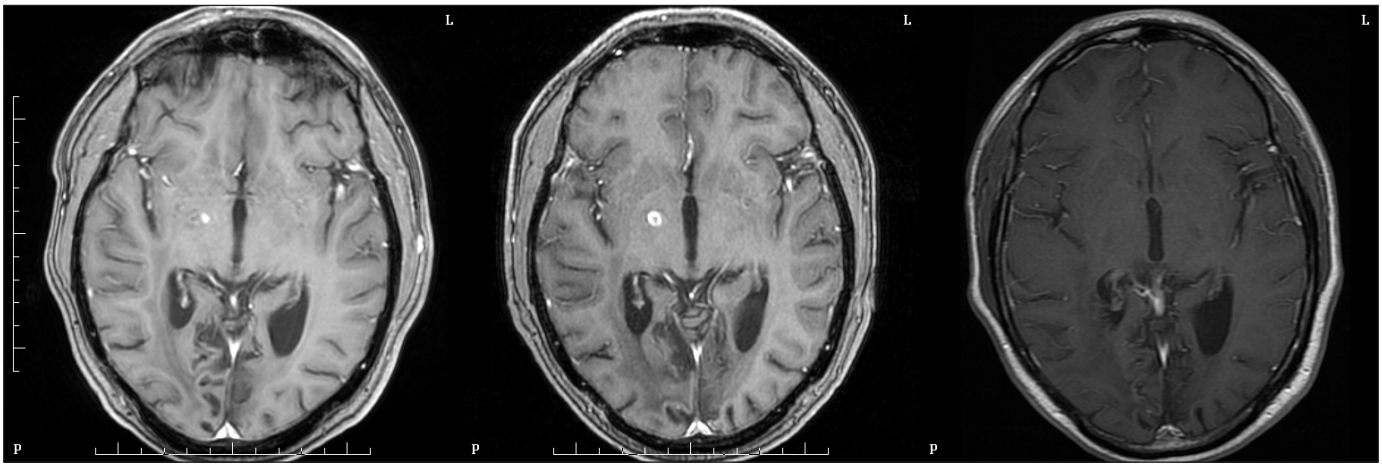

Figure 1: *Axial T1-gadolinium enhanced MRI of patient 3, two months and the week (left, center) prior to initiating PCB-TMZ (increased choline peak on spectroscopy not shown) and five months (right) following initiation of PCB-TMZ.*

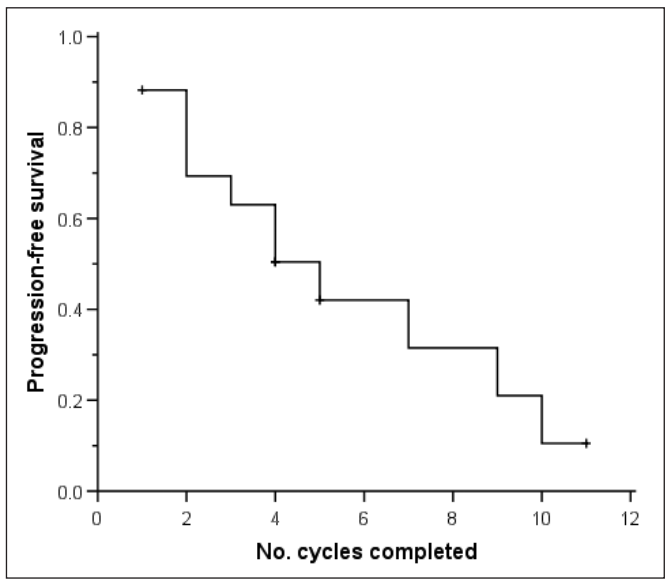

Figure 2: *Progression-free survival from the time of initiation of PCB-TMZ.*

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methylated (1 CR and 1 PR) and unmethylated (1 PR) profiles. Because of the small patient numbers no statistical analyses were performed.

Discussion

Both TMZ and PCB are oral prodrugs with alkylating properties. Temozolomide is rapidly converted at physiologic pH to its active metabolite, monomethyl triazenoimidazole carboxamide (MTIC), which methylates DNA at the O^6 and N^7 positions of guanine. As DNA becomes methylated, cytotoxic cross-links are formed at the guanine bases, in all phases of the cell cycle. While the anti-cancer properties of PCB were described by Bollag in 1963,[15] the mechanism of action has yet to be fully understood. There is evidence for inhibition of protein synthesis, via t-RNA transmethylation inhibition. Oxidative DNA damage, via free-radical intermediates such as hydrogen peroxide generated during auto-oxidation of PCB to its azo form, has also been proposed. However a predominantly alkylating action is presumed. This effect is S-phase specific.[16]

PCB may lack cross-resistance with conventional alkylating agents and has been used in the combination treatment PCV. Most reports of single-agent salvage PCB for glioma describe prior chemotherapy exposure. In one European Organisation for Research and Treatment of Cancer (EORTC) trial, 17 glioma patients relapsed during CCNU-teniposide treatment after surgery and EBRT. Each patient completed at least one 21-day course of salvage PCB (150-200 mg/day), without any clinical improvement lasting six weeks or more.[17] Rodriguez et al[18] reviewed 99 cases of recurrent malignant glioma. All had prior EBRT, and 96% failed prior nitrosurea chemotherapy. After oral PCB (130-150 mg/m^2/day for 28 days, every eight weeks), a 28% response rate was seen, with median TTP of 30 and 49 weeks for GBM and anaplastic glioma, respectively. In contrast, Newton et al[19] reported 57% overall response with oral PCB (65-150 mg/m^2/day for 28 days, every eight weeks) in 35 patients with recurrent astrocytoma after radiation and nitrosurea failure. Over one-third had prior exposure to PCB (400-500 mg) as a chemosensitizer pre-BCNU. After two courses, there were 2 CR (lasting 11 and 12+ months), defined as resolution of all CT abnormalities and improved neurological examination off steroids. Mean TTP was 13.8 months in those with PR. One recent dose-escalation study evaluating PCB pharmacokinetics in recurrent glioma (93% high grade), at least three months post-radiotherapy, reported on an oral regimen of 200-429 mg/m^2/day for five days, every 28 days.[20] There were no CR, and the overall response was 8%, with response defined as above. Median TTP was two months and overall survival 6.5 months.

One phase I trial evaluated PCB and TMZ as combined treatment for gliomas progressing after adjuvant radiation. All 28 patients were chemo-naive, and received an initial test course of TMZ (200 mg/m^2/day for five days), prior to initiating the regimen of TMZ (150-200 mg/m^2/day for five days) with escalating doses of PCB (50-125 mg/m^2/day for five days) in 28-day cycles. Although the study was interrupted prematurely, an overall response rate of 36% was seen, with TTP ranging from 2 to 17+ months. PCB-TMZ in this case was generally well tolerated, except for lethargy, malaise, and few cases of thrombocytopenia reported with the higher PCB dose.[21] The lack of significant toxicity from our range of PCB dosing suggested that a 150 mg/m^2/day dose could be offered to a well-monitored population.

How PCB may potentiate the effects of TMZ in recurrent malignant glioma failing TMZ alone is uncertain. Both are known to methylate DNA, causing lethal methylguanine adducts. These are targeted by MGMT, which irreversibly removes a single methyl group from the O^6 position of guanine.[22] Methylation of the MGMT promoter in tumor DNA is an independent and stronger prognostic factor than age, stage, tumor grade, or performance status in predicting the response of gliomas to alkylating agents.[14] Our own MGMT promoter methylation profiles fail to predict any difference in outcome after PCB-TMZ. This is likely due to our small sample size rather than a negating effect of this combination regimen on the prognostic power of MGMT promoter methylation. Indeed patients with methylated promoters were over-represented in our series, possibly reflecting the selection pressures of prior treatment regimens.

In evaluating a combination treatment used in hopes of increasing tumor cell cytotoxicity, normal tissue toxicities must also be considered. Nausea and vomiting have been reported in over 90% of TMZ-treated patients, usually of rapid onset and short-lived. Myelosuppression associated with TMZ is typically mild to moderate. As an MTIC prodrug, TMZ may also be expected to cause, rarely, flu-like symptoms, hepatotoxicity, alopecia, facial flushing, neurological or dermatological reactions. With PCB, leukopenia and thrombocytopenia are the most commonly reported side effects, generally beginning in the second week of a 10-14 day regimen, and reversing within two weeks off treatment. Hypersensitivity can occur, and may mediate rare pulmonary toxicity. Less than 10% of patients may encounter PCB-related gastrointestinal, neurological and dermatological effects.[16,22] Although there was unexpected severe hepatotoxicity in a Phase I study of PCB alone for recurrent glioma,[20] all three cases were associated with doses higher than those used in clinical practice in addition to concurrent enzyme-inducing drugs. No cumulative end-organ toxicity has been demonstrated to limit TMZ re-use in patients failing TMZ alone. With the possbility of overcoming drug resistance using a combination of oral alkylating agents we were able to continue using TMZ in previously exposed patients.

Conclusion

In this first report of PCB and repeat TMZ in the salvage treatment of glioma, a modest response was achieved without dose-limiting toxicity. Previously described toxicities, which have discouraged the use of single-agent PCB, were not seen in our patients, and were likely dose- and schedule-driven. While our experience is limited, we propose this easily administered oral regimen of PCB-TMZ to be a treatment alternative to consider for post-TMZ failures in patients for which no clinical trial is available.

References

1. Stupp R, Hegi ME, van den Bent MJ, Mason WP, Weller M, Mirimanoff RO, et al. Changing paradigms--an update on the multidisciplinary management of malignant glioma. Oncologist. 2006 Feb;11(2):165-80.

https://doi.org/10.1017/S0317167100008623 Published online by Cambridge University Press

2. Brandes AA, Tosoni A, Basso U, Reni M, Valduga F, Monfardini S, et al. Second-line chemotherapy with irinotecan plus carmustine in glioblastoma recurrent or progressive after first-line temozolomide chemotherapy: a phase II study of the Gruppo Italiano Cooperativo di Neuro-Oncologia (GICNO). J Clin Oncol. 2004 Dec 1;22(23):4779-86.
3. Rabik CA, Njoku MC, Dolan ME. Inactivation of O6-alkylguanine DNA alkyltransferase as a means to enhance chemotherapy. Cancer Treat Rev. 2006 Jun;32(4):261-76.
4. Brandes AA, Reni M. Treatment options for recurrent glioblastoma. PCNSM2– Perspectives in central nervous system malignancies. Budapest, Hungary; 2006.
5. Khan RB, Raizer JJ, Malkin MG, Bazylewicz KA, Abrey LE. A phase II study of extended low-dose temozolomide in recurrent malignant gliomas. Neuro-oncol. 2002 Jan;4(1):39-43.
6. Tosoni A, Cavallo G, Ermani M, Scopece L, Franceschi E, Ghimenton C, et al. Is protracted low-dose temozolomide feasible in glioma patients? Neurology. 2006 Feb 14;66(3):427-9.
7. Berrocal A, Perez-Segura P, Gil M, Balaña C, Yaya-Tur R, Yaya-Tur R, et al. Phase II study of extended schedule temozolomide in refractory gliomas. J Clin Oncol. 2006;24(18S):1516.
8. Vera K, Djafari L, Faivre S, Guillamo JS, Djazouli K, Osorio M, et al. Dose-dense regimen of temozolomide given every other week in patients with primary central nervous system tumors. Ann Oncol. 2004 Jan;15(1):161-71.
9. Koch D, Wick W. Higher dosing of temozolomide? Regression of an anaplastic oligoastrocytoma over more than three years. J Neurooncol. 2006 Apr;77(2):219-20.
10. Spence AM, Kiem HP, Partap S, Schuetze S, Silber JR, Peterson RA. Complications of a temozolomide overdose: a case report. J Neurooncol. 2006 Oct;80(1):57-61.
11. Franceschi E, Omuro AM, Lassman AB, Demopoulos A, Nolan C, Abrey LE. Salvage temozolomide for prior temozolomide responders. Cancer. 2005 Dec 1;104(11):2473-6.
12. Groves MD, Puduvalli VK, Conrad CA, Gilbert MR, Yung WK, Jaeckle K, et al. Phase II trial of temozolomide plus marimastat for recurrent anaplastic gliomas: a relationship among efficacy, joint toxicity and anticonvulsant status. J Neurooncol. 2006 Oct;80(1):83-90.
13. Raizer JJ, Abrey LE, Wen P, Cloughesy T, Robins IA, Fine HA, et al. A phase II trial of erlotinib (OSI-774) in patients with recurrent malignant gliomas not on EIAEDs. 2004 ASCO Annual Meeting; 2004; New-Orleans, Louisiana: J Clin Oncol. 2004; p. 1502.
14. Esteller M, Garcia-Foncillas J, Andion E, Goodman SN, Hidalgo OF, Vanaclocha V, et al. Inactivation of the DNA-repair gene MGMT and the clinical response of gliomas to alkylating agents. N Engl J Med. 2000 Nov 9;343(19):1350-4.
15. Bollag W. The tumor-inhibitory effects of the methylhydrazine derivative Ro 4-6467/1 (Nsc-77213). Cancer Chemother Rep. 1963 Dec;33:1-4.
16. Goodman & Gilman's The pharmacological basis of therapeutics. 11th ed. New York: McGraw-Hill; 2006.
17. European Organization for Research on Treatment of Cancer (EORTC) Brain Tumor Group. Evaluation of CCNU, VM-26 plus CCNU, and procarbazine in supratentorial brain gliomas. Final evaluation of a randomized study. J Neurosurg. 1981 Jul; 55(1):27-31.
18. Rodriguez LA, Prados M, Silver P, Levin VA. Reevaluation of procarbazine for the treatment of recurrent malignant central nervous system tumors. Cancer. 1989 Dec 15;64(12):2420-3.
19. Newton HB, Junck L, Bromberg J, Page MA, Greenberg HS. Procarbazine chemotherapy in the treatment of recurrent malignant astrocytomas after radiation and nitrosourea failure. Neurology. 1990 Nov;40(11):1743-6.
20. Grossman SA, Carson KA, Batchelor TT, Lesser G, Mikkelsen T, Alavi JB, et al. The effect of enzyme-inducing antiseizure drugs on the pharmacokinetics and tolerability of procarbazine hydrochloride. Clin Cancer Res. 2006 Sep 1;12(17):5174-81.
21. Newlands ES, Foster T, Zaknoen S. Phase I study of temozolamide (TMZ) combined with procarbazine (PCB) in patients with gliomas. Br J Cancer. 2003 Jul 21;89(2):248-51.
22. DeVita VT Jr, Hellman S, Rosenberg S, editors. Cancer principles & practice of oncology. 7th ed. Philadelphia: Lippincott Williams & Wilkins; 2005.