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Abstract: For more than three decades, alkylating agents have been the most widely used class of chemotherapeutic agents for the treatment of glial brain tumors. Today, concomitant and adjuvant temozolomide is the standard of care for newly diagnosed glioblastoma. Temozolomide alone or in combination with radiotherapy is being explored in ongoing trials in newly diagnosed patients with low-grade and anaplastic glioma. Rechallenge with alternative dosing schedules of temozolomide is a valid treatment option in recurrent, temozolomide-pretreated patients with glioblastoma, and nitrosourea compounds are alternative treatment options in this setting, in addition to novel, mostly antiangiogenic agents, notably bevacizumab. Moreover, nitrosoureas have become the gold standard comparator arm for the evaluation of novel treatments in recurrent glioblastoma.

Optimizing the Use of Alkylators in Neuro-oncology

By James R. Perry, MD, Wolfgang Wick, MD, and Michael Weller, MD

Overview: **For more than three decades, alkylating agents have been the most widely used class of chemotherapeutic agents for the treatment of glial brain tumors. Today, concomitant and adjuvant temozolomide is the standard of care for newly diagnosed glioblastoma. Temozolomide alone or in combination with radiotherapy is being explored in ongoing trials in newly diagnosed patients with low-grade and anaplastic glioma. Rechallenge with alternative dosing schedules of temozolomide is a valid treatment option in recurrent, temozolomide-pretreated patients with glioblastoma, and nitrosourea compounds are alternative treatment options in this setting, in addition to novel, mostly antiangiogenic agents, notably bevacizumab. Moreover, nitrosoureas have become the gold standard comparator arm for the evaluation of novel treatments in recurrent glioblastoma.**

UNTIL THE past decade the use of chemotherapy for low- and high-grade gliomas was mostly restricted to salvage therapy following initial surgery and radiotherapy. Clinical trials testing the role of adjuvant chemotherapy in grade 3 and 4 gliomas showed minimal benefit with agents such as the nitrosoureas and, perhaps surprisingly, even the use of both neoadjuvant and adjuvant procarbazine, lomustine (CCNU), and vincristine (PCV) chemotherapy failed to show improved overall survival in the most chemosensitive subtypes of glioma.[1,2]

In 2005, a pivotal European Organisation for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG), trial tested the incorporation of temozolomide concurrent with radiotherapy followed by six maintenance cycles of adjuvant chemotherapy for newly diagnosed glioblastoma.[3] The study found improved survival with benefit extending for several years and set both a new standard of care and a new clinical trials platform for the optimization of temozolomide/radiotherapy in glioblastoma. In a subset analysis of patients from this study, the clinical benefit was found to be mainly restricted to patients harboring promoter methylation of the DNA repair gene O^6-methylguanine-DNA methyltransferase (*MGMT*), a key mechanism of *MGMT* gene silencing that predicts a favorable outcome to combined-modality therapy.[4] The MGMT biomarker is currently used as an important stratification variable in new clinical trials, such as Radiation Therapy Oncology Group (RTOG) 0525, or even to select patients for clinical trials, such as the CENTRIC study, which compares radiotherapy plus temozolomide with or without concomitant cilengitide, an integrin inhibitor with promising activity and an excellent safety profile. At present, the MGMT biomarker is not sufficiently characterized to be used to select patients for alkylator chemotherapy; however, several ongoing prospective studies will soon be completed and will clarify the role of MGMT as a predictive versus prognostic biomarker and the role of routine testing in clinical practice.[5]

Ongoing clinical trials now incorporate 60 Gy external beam radiotherapy with concomitant temozolomide (75 mg/m^2 orally, daily, for 6 weeks, including weekends) and are exploring the additive value of additional cytotoxic, cytostatic, and targeted therapies. The most ambitious of these trials include the cilengitide program for patients with *MGMT*-methylated tumors (phase III); schedule-intensified cilengitide for *MGMT*-unmethylated tumors (phase II); the addition of bevacizumab to standard upfront and adjuvant therapy (AvaGlio trial); and RTOG 0825 (phase III). Other studies seek to clarify the optimal duration and schedule of adjuvant chemotherapy. RTOG 0525 is expected to have early results available by the 2011 ASCO Annual Meeting and may clarify the optimal schedule for adjuvant temozolomide use (conventional 150–200 mg/m^2 5-day therapy vs. 75 mg/m^2 21-day therapy in an extended regimen) and may also provide a wealth of prospective information on MGMT and other important biomarkers and genetic profiles in newly diagnosed glioblastoma.

For patients with anaplastic gliomas the addition of cytotoxic chemotherapy with agents such as temozolomide to initial therapy is controversial. One can argue that if the radiotherapy/temozolomide approach is beneficial in the least chemosensitive type of glioma (glioblastoma), then it should also be beneficial for grade 3 gliomas such as anaplastic astrocytoma and, especially, anaplastic oligodendroglioma harboring loss of heterozygosity of 1p and 19q. Unfortunately, there is currently no level 1 evidence on which to base such a treatment recommendation. Furthermore, for patients with survival times that can exceed a decade, the long-term toxicities of currently available therapies are poorly understood, and chemotherapy alone has been identified as a promising alternative option for many patients with anaplastic gliomas.[6]

Two recently developed clinical trials conducted through international collaboration will help to answer some of these questions for anaplastic gliomas. EORTC 26053 (NCIC-CTG CEC.1, RTOG 0834) is a phase III randomized trial of radiotherapy with or without concomitant temozolomide, and with or without adjuvant temozolomide, in patients with newly diagnosed anaplastic gliomas without 1p or 19q deletions. This study should help to dissect the benefit of the concomitant portion of temozolomide therapy from the adjuvant portion, compared with both together versus none at all. In comparison, for the same histologic tumors (anaplastic glioma) but with codeletion of 1p and 19q, a companion phase III randomized trial consists of three arms: 1) standard radiotherapy alone; 2) standard radiotherapy with

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Table 1. Activity of Temozolomide Rechallenge or Nitrosoureas in Patients with Recurrent Glioblastoma Pretreated with Temozolomide: Comparison with Antiangiogenic Agents

	Treatment	CR + PR (%)	Median Progression-free Survival (weeks)	Progression-free Survival at 6 months (%)	Median Survival (weeks)
Progression during temozolomide					
Perry et al. 2010[16] (n = 33)	Temozolomide 28/28	3	15	27	Nd
Wick et al. 2009[13] (n = 19)	Temozolomide diverse	0	18	26	23
Progression after temozolomide					
Perry et al. 2010[16] (n = 28)	Temozolomide 28/28	11	16	36	Nd
Wick et al. 2009[13] (n = 28)	Temozolomide diverse	17	21	29	29
Nitrosoureas					
Van den Bent et al. 2009[27] (n = 56)	BCNU/temozolomide	10	10	24	31
Wick et al. 2010[24] (n = 92)	CCNU	4	7	19	30
Batchelor et al. 2010[26] (n = 65)	CCNU	9	12	25	44
Antiangiogenic agents					
Kreisl et al. 2009[17] (n = 48)	Bevacizumab	35	16	29	31
Friedman et al. 2009[11] (n = 85)	Bevacizumab	28		43	39
Batchelor et al. 2010[26] (n = 31)	Cediranib	57	17	26	32
Wick et al. 2010[24] (n = 174)	Enzastaurin	3	6	11	28

Abbreviations: CR, complete response; PR, partial response; BCNU, carmustine; CCNU, lomustine.

concomitant and adjuvant temozolomide; and 3) temozolomide chemotherapy alone in the conventional 5-day schedule (NCCTG-N0557, EORTC 26081–22086). Both of these collaborative studies include robust molecular substudies.

The role of chemotherapy in low-grade gliomas remains controversial. Although it is clear that some patients with low-grade gliomas respond to chemotherapy, the optimal timing, drug, and schedule of administration is unclear, especially for newly diagnosed patients. Buckner and colleagues reported a phase II trial of upfront PCV chemotherapy followed by radiotherapy at completion or during progression on chemotherapy and noted tumor regression in 52% (13 of 25 patients).[7] In RTOG 9802, 251 patients with lograde gliomas were randomly assigned to radiation therapy alone versus radiation followed by six cycles of PCV.[8] An advantage in both progression-free and overall survival favored the PCV arm; however, PCV resulted in significant toxicity in some patients. Because of the widespread use of temozolomide, there have been several trials exploring the role of upfront temozolomide in patients with low-grade glioma. Quinn and colleagues offered temozolomide at 200 mg/m^2 in the conventional 5-day cycle to treatment-naive patients with progressive low-grade glioma and saw an objective response rate of 61% with a median progression-free survival of 22 months.[9] Others have explored the use of protracted temozolomide (75 mg/m^2/day for 21 days), finding prolonged overall survival in patients with *MGMT* promoter methylation.[10,26] These studies demonstrate biologic activity of alkylator-based treatment of low-grade gliomas, but add little to our understanding of the optimal type and timing of treatment for these patients.

Future development of temozolomide and other nonradiotherapy strategies for patients with low-grade glioma will be enhanced by the development of improved response assessment guidelines (an ongoing project of the Response Assessment in Neuro-Oncology group) and discovery and validation of current (MGMT, 1p/19q codeletion, isocitrate dehydrogenase 1/2) and future biomarkers. Two ongoing phase III trials are designed explore these questions. In EORTC 22033 to 26033, NCIC-CTG CE.5, patients with symptomatic or progressive low-grade glioma are stratified according to 1p/19q codeletion and randomly assigned to either 50.4 Gy radiotherapy alone versus temozolomide alone (75 mg/m^2/day for 21 days). In a complementary trial administered by the Eastern Cooperative Oncology Group, as many as 540 patients with known 19/19q status and symptomatic or progressive low-grade glioma will be randomly assigned to either radiotherapy or radiotherapy with concurrent temozolomide followed by up to 12 cycles of adjuvant temozolomide in the conventional 5-day schedule. These two trials are poised to help understand the efficacy and longer-term toxicity of therapy in these patients.

KEY POINTS

- Concomitant and adjuvant temozolomide is the standard of care for newly diagnosed glioblastoma.
- Temozolomide alone or in combination with radiotherapy ise being explored in ongoing trials in newly diagnosed patients with low-grade and anaplastic glioma.
- Rechallenge with alternative dosing schedules of temozolomide is a valid treatment option in recurrent, temozolomide-pretreated glioblastoma.
- Nitrosoureas have become the gold standard comparator arm for the evaluation of novel treatments in recurrent glioblastoma.

Alternative Dosing Schedules of Temozolomide at Recurrence of Temozolomide-pretreated Gliomas

No standard of care has been defined for patients with glioblastoma who relapse or progress on or after standard temozolomide-based radiochemotherapy. A minority of patients will undergo second surgery; few patients are eligible for re-irradiation. The most commonly used pharmacologic agents administered at recurrence are nitrosoureas, the vascular endothelial growth factor (VEGF) antibody, bevacizumab, and a rechallenge with temozolomide.[11-13] These approaches are summarized and compared in Table 1. Patients with a treatment-free interval between the end of adjuvant temozolomide and recurrence can be treated with the standard 5 out of 28-days regimen. However, even for these patients, and for all patients who experience treat-

ment failure on, rather than after, standard adjuvant temozolomide, various dose-intensified regimens of temozolomide are being used, including: 1) 3 weeks on 1 week off, 2) 1 week on 1 week off, or 3) continuous application, as exemplified in the RESCUE concept.[14-16]

It has not been clarified which temozolomide rechallenge regimen is most effective and tolerable in recurrent glioblastoma and whether the dose-intensified regimens overcome chemoresistance mediated by the absence of *MGMT* promoter methylation. In recurrent glioblastoma, the prognostic value of the *MGMT* status has remained unclear.

The progression-free survival rates at 6 months were in the range of 30% or more for bevacizumab in the phase II trials that led to registration, and 20% for nitrosoureas in clinical trials where these agents served as the control arm (see below).[11,17] The progression-free survival rate at 6 months was 25% in the RESCUE trial, which explored low continuous dosing of temozolomide at 50 mg/m^2 for patients recurring during or after adjuvant temozolomide.[16] The DIRECTOR trial is a prospective, randomized, noncomparative, open-label phase II trial that assesses the efficacy of the 1 week on 1 week off (120 mg/m^2) and the 3 weeks on 1 week off (80 mg/m^2) regimens in patients with glioblastoma who progress or relapse after standard first-line temozolomide radiochemotherapy and at least two cycles of adjuvant temozolomide. The primary endpoint is time-to-treatment failure defined as progression, intolerability of study treatment, or death as a result of any cause. Secondary endpoints are progression-free survival, overall survival, response and *MGMT* correlations.

The Re-emerging Role of Nitrosourea Compounds in the Treatment of Progressive or Recurrent Gliomas

The use of older generation alkylating agents of the nitrosourea family has experienced major changes in neuro-oncology during the last 10 years. Approximately 30 years ago, after radiotherapy had been defined as the best standard of care after surgery, the major interest was to define a role for adjuvant chemotherapy in addition to radiotherapy using various agents of that family, including carmustine, CCNU, nimustin.[18,19] Although none of these studies had sufficient data quality—by modern standards—to demonstrate the efficacy of adjuvant nitrosourea chemotherapy, there was still a broad consensus that the chances of long-term survival were increased by adjuvant chemotherapy, albeit at the prize of significant hematologic toxicity.[18]

When temozolomide was approved for recurrent glioblastoma in Europe (although not in the United States), an alkylating drug had, for the first time, found a well-defined place in the treatment of recurrent glioblastoma.[20] Moreover, temozolomide was also approved for recurrent anaplastic gliomas both in Europe and in the United States.[21] In 2005, when temozolomide was approved for newly diagnosed glioblastoma, the general interest in chemotherapy for glioblastoma increased, and was associated with an increasing use, or at least appreciation, of the role of nitrosourea compounds for recurrent disease.[3] In a world where glioblastoma patients were now eligible for any treatment at recurrence, most had already been exposed to temozolomide upfront.

Various uncontrolled studies using the above-mentioned compounds demonstrated higher hematologic toxicity in patients pretreated with temozolomide and progression-free survival rates in the range of 20%.[22] Nevertheless, outside clinical trials, such agents became a standard of care, especially in countries where the option to explore alternative dosing schedules of temozolomide outside clinical trials is limited. Of note, only two trials have directly compared nitrosourea-based regimens with temozolomide without demonstrating differences in efficacy; the German NOA-04 trial identified similar efficacy, but less hematologic toxicity, of temozolomide compared with the combination of PCV in patients with newly diagnosed anaplastic gliomas, and the British BR-12 trial reported similar efficacy and toxicity of both regimens in chemotherapy-naive patients with recurrent grade 3/4 gliomas.[6,23]

Although the design of many trials performed in the recurrent glioblastoma setting indicated that the efficacy of nitrosoureas was considered to be rather low, various promising new agents experienced an impressive failure to demonstrate superiority over nitrosoureas, mostly CCNU, as demonstrated by the failed registration trials for enzastaurin, tradedersen, or cediranib, or the randomized phase II trial for erlotinib performed by the EORTC.[24-27] Notably, the failure of the most potentially promising of these agents, cediranib, has defined for the modern area of glioblastoma trials that lomustine is an acceptable control arm for randomized trials at recurrence. The unexpected outcome of the cediranib trial has also facilitated the consensus that a controlled trial randomizing lomustine and the VEGF antibody bevacizumab, and combinations thereof, as currently planned by the EORTC, is worthwhile.

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