Standard Therapy for Glioblastoma—
A Review of Where We Are

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Abstract

Glioblastoma is the most common primary malignant brain tumor in adults and is a challenging disease to treat. The current standard therapy includes maximal safe surgical resection, followed by a combination of radiation and chemotherapy with temozolomide. However, recurrence is quite common, so we continue to search for more effective treatments both for initial therapy and at the time of recurrence. This article will review the current standard of care and recent advances in therapy for newly-diagnosed and recurrent glioblastomas, based on the most authoritative guidelines, the National Cancer Institute’s comprehensive cancer database Physician Data Query (PDQ®), and the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology™ for central nervous system cancers (V.1.2010), to elucidate the current position and in what direction we are advancing.

Key words: glioblastoma, standard therapy, chemotherapy, temozolomide, clinical trial

Definition of Standard Therapy

Standard therapy is the treatment that experts agree is appropriate, accepted, and widely used, and is also called best practice and standard of care. Health care providers are obligated to provide patients with standard therapy. Physicians are not allowed to provide patients with non-standard therapy without explaining the reason why standard therapy will not be provided and obtaining informed consent. Every clinical trial should have a convincing scientific basis to indicate that testing the treatment is worthwhile, and the patients should be informed that the test treatment is not a standard therapy, which is requisite from an ethical point of view. The Institutional Review Board (IRB) will examine the protocols, case report forms, and related documents from both scientific and ethical points of view. In randomized phase 3 studies, the control arms are always standard therapies of the diseases.

Standard Therapy for Glioblastoma in Physician Data Query (PDQ®)

PDQ® is the National Cancer Institute’s comprehensive cancer database, and is the most authoritative guideline. PDQ® is written in an itemized manner, so needs some commentary and explanations (Table 1).

Table 1 Standard therapy for glioblastoma in PDQ®

<table>
<thead>
<tr>
<th>Therapy Description</th>
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<tr>
<td>Surgery plus radiation therapy for elderly glioblastoma patients</td>
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<tr>
<td>No additional benefit from brachytherapy added to external-beam radiation therapy</td>
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<tr>
<td>and carmustine (BCNU)</td>
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<tr>
<td>BCNU-impregnated polymer (Gliadel wafer) implanted during initial surgery</td>
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<tr>
<td>Radiation therapy and concurrent chemotherapy with temozolomide</td>
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PDQ®: Physician Data Query.

The first point is the treatment of glioblastoma (GBM) in the elderly population. Since the landmark European Organization for the Research and Treatment of Cancer (EORTC)/National Cancer Institute of Canada (NCIC) study published in 2005, the standard therapy for GBM has been post-operative adjuvant radiotherapy with concomitant and adjuvant temozolomide (TMZ) (so-called Stupp’s regimen). However, the patients eligible for this study were aged from 18 to 70 years, so the standard therapy for GBM patients aged over 70 years remains undetermined. Because the frequency of severe adverse events of TMZ is less than 10%, and the pharmacokinetic profile of TMZ is not age-dependent, investigators surmise that Stupp’s regimen would be applicable for elderly patients, but this notion has not actually been proven yet.

A randomized phase 3 study comparing postoper-
ative supportive care and postoperative radiation therapy plus supportive care was performed for GBM patients over 70 years old.\textsuperscript{10} The median survival time was 29.1 weeks for the 39 patients who received radiation therapy plus supportive care and 16.9 weeks for the 42 patients who received only supportive care. The hazard ratio of death in the radiation therapy arm was 0.47 (95% confidence interval [CI] 0.29–0.76; \( p = 0.002 \)). This study was discontinued prematurely at the first interim analyses, because the radiotherapy plus supportive care arm was superior to the only supportive care arm with a preset boundary of efficacy. Post-operative radiotherapy resulted in a robust improvement in survival in elderly patients with GBM, and is now the standard therapy for this population. To prove that a full dose of 60 Gy/30 fractions was necessary for elderly GBM patients, a randomized study of patients 60 years and older comparing post-operative radiotherapy of 60 Gy/30 fractions (standard course) and 40 Gy/15 fractions administered over the course of 3 weeks (short course) was performed. Overall survival (OS) was similar for the two groups; 5.1 months for the standard course arm, and 5.6 months for the short course arm (\( p = 0.57 \)).\textsuperscript{22} Although there was concerns about the power of the study, which was discontinued prematurely at the first interim analysis when 100 patients were recruited, the results showed the outcomes of the two arms were statistically equivalent, so the short course of radiotherapy seemed to be the reasonable treatment option for elderly patients with GBM.

Deterioration of cognitive function is a well known adverse effect of radiotherapy, especially in the elderly population. Treatment with only TMZ, without radiotherapy, may be equivalent in OS and would provide better health-related quality of life (QoL), which is a reasonable hypothesis to be tested in elderly GBM patients. Three randomized phase 3 studies for elderly GBM patients are on-going: a three-arms study by the Nordic Clinical Brain Tumor Group assessing the efficacy of short course radiotherapy and only TMZ arms with standard course radiotherapy of 60 Gy; a study by the German Neuro-Oncology Working Group simply testing the efficacy of only TMZ treatment versus the standard course of radiotherapy, and the study by NCIC and EORTC aiming at the assessment of the additive effect of TMZ to short course radiotherapy. Three institutes from Japan, Kitano Hospital, Hiroshima University, and the International Medical Center, Saitama Medical University are members of the international study group for the NCIC/EORTC study, CE.6. Conclusions from these studies will decide if only TMZ is equivalent to radiotherapy, and provides better QoL, and if concomitant and adjuvant TMZ with short course radiotherapy would be valuable for elderly GBM patients.

The second point in PDQ\textsuperscript{E} is evaluation of the efficacy of brachytherapy for GBM. A randomized cooperative study showed no additional benefit from brachytherapy added to external-beam radiation therapy and carmustine (BCNU) (NIH Trial 87-01).\textsuperscript{23} Interstitial brachytherapy is one of the techniques to deliver high doses of irradiation to the tumor beds. Stereotactic radiotherapy is another high-dose local radiotherapy technique, which also failed to show survival advantage compared to external beam irradiation in a phase 2 study by the Radiation Therapy Oncology Group (RTOG 0023).\textsuperscript{4} Because of the highly invasive nature of GBM, however high the irradiated dose is, the effect of radiotherapy would be limited as the irradiated field is restricted to the enhanced lesion.

The third point in PDQ\textsuperscript{E} is the evaluation of BCNU-impregnated polymer (Gliadel\textsuperscript{E} wafer) implanted during surgeries. A multicenter randomized double-blinded controlled trial with 240 patients with high-grade glioma including 207 GBM and 21 anaplastic glioma reported significantly longer OS for patients who had Gliadel\textsuperscript{E} wafer placed intraoperatively (13.8 months for Gliadel\textsuperscript{E} wafers vs. 11.6 months for placebo; HR 0.73, 95% CI 0.56–0.95; \( p = 0.0018 \)).\textsuperscript{32} However, a subanalysis of 207 GBM patients could not show significantly longer survival with Gliadel\textsuperscript{E} wafer (13.1 months in the Gliadel\textsuperscript{E}-treated group and 11.4 months in the placebo-treated group, \( p = 0.08 \)). The spacial and temporal distribution of BCNU released from the polymer was calculated by a mathematical simulation model.\textsuperscript{31} The penetration depth of BCNU from a polymer was estimated to be 0.5 cm. The penetration depth was defined as the average distance measured from the surface of a polymer at which the drug concentration is 1% compared to that of the polymer surface. The distance of penetration is short because BCNU has a high transvascular permeability and, therefore, is very easily absorbed into the systemic circulation. BCNU molecules, being lipid-soluble and very permeable, enter the bloodstream before they can travel far. Together with the short half life of BCNU (1.5 hours), the short distance of penetration would limit the efficacy of the therapy.

The last point in PDQ\textsuperscript{E} is radiation therapy and concurrent chemotherapy. A randomized study performed by EORTC and NCIC was a landmark of GBM treatment. Radiation therapy plus TMZ followed by 6 months of adjuvant TMZ in patients with newly diagnosed GBM demonstrated a statistically significant survival advantage over simple...
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hydrochloride (ACNU) was widely used based on a
small randomized study in Japan in the 1980s.26) The
response rate was better in the combined treatment
arm with ACNU and radiotherapy (47.5% in the
combined treatment arm, 13.5% in the simple
radiotherapy arm), but the OS was not significantly
different (median OS was 14 months and 12 months,
respectively). Although the combined therapy with
ACNU and radiotherapy was promising, a ran-
domized phase 3 study had not been performed.
Nevertheless, without a phase 3 study, the combina-
tion of ACNU and radiotherapy was adapted as the
standard therapy for malignant gliomas in Japan. The
brain tumor study group of JCOG considered
this as the community standard of GBM therapy that
was made the starting point.

The JCOG 0305 study was a randomized phase 2
study comparing two combined-treatment pro-
tocols, ACNU with radiotherapy and procarbazine
(PCZ) plus ACNU with radiotherapy. In the PCZ
plus ACNU arm, PCZ was administered before
ACNU aiming to deplete MGMT and to enhance the
chemosensitivity to ACNU,24) When the phase 2
study cleared a preset boundary of efficacy, the
phase 3 study would begin, which was the original
design. However, an interim analysis revealed there
was no survival advantage of the test arm. This study
was discontinued and did not proceed to phase 3.
The control arm, ACNU with radiotherapy,
achieved a median OS of 16.6 months for GBM,
which should have been the basic data for the clini-
cal trials for GBM thereafter in Japan. In 2005, the
results of the combination of TMZ and radiotherapy
were published as previously mentioned, and the
combination of TMZ and radiotherapy became the
standard therapy of GBM worldwide. No ran-
domized comparison of ACNU and TMZ has been
considered so far, based on the following reasoning.

Is ACNU Only a Memory?

In 2000, the Japan Clinical Oncology Group (JCOG)
brain tumor study group was discussing how to initi-
ate clinical studies for brain tumors in Japan. One of
the foci of the discussion was the standard therapy
for GBM at that time. 1-(4-Amino-2-methyl-5-
pirimidinyl)-methyl-3-(2-chloroethyl)-3-nitrosourea
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considered so far, based on the following reasoning.
The HR for death in the radiotherapy plus TMZ arm was 0.63 (95% CI 0.52–0.75; p < 0.001). Meta-analysis evaluating the effectiveness of nitrosoureas (mainly BCNU) found the HR was 0.85 (95% CI 0.78–0.91; p < 0.0001). Considering the 95% CI, nitrosoureas were not thought to be as good as TMZ. The OS and PFS for GBM patients treated with concomitant and adjuvant TMZ with radiotherapy were 14.6 months and 6.9 months, respectively, whereas those with ACNU and radiotherapy were 16.6 months and 5.1 months based on the JCOG study, respectively. The better OS with ACNU and radiotherapy in Japan was possibly related to salvage therapies including repeat surgeries and stereotactic radiosurgeries, and to elaborate supportive care. The better OS with ACNU treatment was not due to better tumor control by ACNU because the PFSs were similar. Another retrospective report comparing BCNU and TMZ also showed that PFS was not significantly different between the two groups. Severe adverse events (CTCAE grade 3 or higher) are more frequent in ACNU-treated patients than in TMZ-treated patients; leucopenia in 39% and 3% of the patients, respectively.

As the next step, the JCOG brain tumor study group has just started a randomized phase 2 study comparing a combination therapy of interferon-β plus TMZ with radiotherapy and a combination therapy of TMZ with radiotherapy, considering the latter as the standard therapy for GBM (JCOG 0911). This strategy is based on data showing the sensitizing effect of IFN-β for TMZ was possibly due to attenuation of MGMT expression via induction of the protein p53.

### When GBM Recurs

The National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology™ is available on-line (http://www.nccn.org). The guideline for central nervous system cancers (V.1.2010) states surgical resection should be considered first if recurrent or progressive tumors are resectable. Systemic chemotherapies are indicated if allowed by the performance status of the patients.

Bevacizumab with or without chemotherapy is the first in the list of possible second line chemotherapies for GBM (Table 2). As we learn more about the biology of GBM and its aberrant signaling pathways, the neuro-oncology community has begun to investigate the role of molecular targeted therapies. The angiogenesis pathways and their associated antiangiogenic agents are the most promising topic recently. Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), was first approved in combination with chemotherapy for colorectal, lung, and breast cancers. Despite initial reluctance to evaluate bevacizumab in patients with brain tumors because of concerns with intracranial hemorrhage, the combination of bevacizumab and irinotecan was studied in a single-arm phase 2 study for recurrent GBM. The response rate was 57%, and PFS at 6 months was 46%. These results compared quite favorably with historical data of response rate of 8% and PFS at 6 months of 21% by TMZ for recurrent GBM. To clarify the contribution of irinotecan, a large phase 2 study randomized 167 patients with recurrent GBM to either single agent bevacizumab or bevacizumab plus irinotecan. The response rates were 28% in the single treatment arm with bevacizumab and 38% in the combination arm of bevacizumab plus irinotecan, and the PFS at 6 months was 43% and 50%, respectively. Curiously enough, the randomized design of the trial was not designed to compare outcomes in the two treatment groups, but to evaluate their superiority to the historical results of salvage chemotherapies, 15% of PFS at 6 months, without bias in treatment assignment. Bevacizumab is usually well tolerated, with the most common adverse effects being hypertension and minor bleeding, such as epistaxis. Intracranial hemorrhage occurred in less than 4% of patients and was severe in only approximately 1% of patients.

Individual infiltrative tumor cells tend to grow along preestablished normal cerebral vasculature, so there is no need for tumor-associated angiogenesis from the tumor cells in the central core. Indeed, there is at least a theoretical concern that inhibiting malignant glioma angiogenesis may have little effect on the infiltrative component of the disease and so little impact on the overall survival of the patient. Furthermore, recent laboratory evidence suggests that inhibition of VEGF may actually increase the invasive nature of tumor cells. There seems to be a proinvasive adaptation to anti-angiogenic therapy, as suggested by magnetic resonance imaging in a subset of GBM patients who developed multifocal

### Table 2 The second-line chemotherapies for recurrent glioblastoma in NCCN guideline

<table>
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<tr>
<td>Temozolomide</td>
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</tr>
<tr>
<td>Nitrosourea or PCV</td>
<td>Nitrosourea or PCV</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Cyclophosphamide</td>
</tr>
<tr>
<td>Platinum-based regimens</td>
<td>Platinum-based regimens</td>
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NCCN: National Comprehensive Cancer Network; PCV: procarbazine, lomustine, and vincristine.
recurrence of tumors during the course of therapy with bevacizumab.\textsuperscript{6,13,17} The infiltrative tumor cells are most often responsible for clinical relapse and ultimately the death of patients with gliomas. Early results from phase 2 trials showed that incorporation of bevacizumab into the standard initial treatment for newly diagnosed GBM increased median PFS, but prolongation of OS is still unclear. Two large phase 3 trials for newly diagnosed GBM are currently randomizing patients to standard radiotherapy and TMZ with or without bevacizumab.

A unique advantage of bevacizumab is the ability to decrease peritumoral edema. Patients treated with bevacizumab often have decreased corticosteroid dependence secondary to neutralization of VEGF, a known vascular permeability factor. Vascular permeability is decreased in and around the tumor, so decreasing both cerebral edema and the uptake of gadolinium within the tumor. An illustrative case (Fig. 1) showed marked decrease of enhancement on MRI after three days of bevacizumab administration. The decrease in enhancement was not due to tumor shrinkage as the enhancement was regained 7 days later (Fig. 1). As such, the remarkable radiographic response rates and PFS by bevacizumab should be interpreted cautiously.

A couple of successful regimens suggested low dose and continuous TMZ administration as a rechallenge was effective for recurrent disease.\textsuperscript{20,33} Due to its usage as the first-line treatment of GBM, TMZ has been no longer considered by many investigators to be a reasonable choice for patients with recurrent GBM. However, alternative schedules of TMZ addressing different pathophysiological mechanisms could be effective even after progression during standard TMZ regimens.\textsuperscript{33} There are several rationales supporting TMZ rechallenge. Firstly, there may be a benefit from alternative modes of action, such as antiangiogenic properties of a metronomic regimen. Secondly, as MGMT is inactivated after each reaction of removal of methyl bases (suicide enzyme), exposure to continuous and low-dose TMZ depletes MGMT activities. Thirdly, the schedule of temozolomide permits a greater drug exposure than the conventional schedule of 5 days every 28 days, with comparable or even lower toxicities.

A “one week on/one week off” scheme (150 mg/m$^2$ at days 1–7 and days 15–21, in a 28-day cycle) has been associated with considerable efficacy and was tolerated by patients. Another alternative is an intensified three out of four weeks approach (75–100 mg/m$^2$ at days 1–21, in a 28 day cycle). This regimen may yield similar results with respect to efficacy, but a higher rate of toxicity, specifically lymphopenia and infection, has been reported. Another regimen is a metronomic administration of TMZ, 20 mg daily.

The third optional treatment for recurrent GBM is regimens containing nitrosoureas, such as procarbazine, lomustine, and vincristine (PCV) chemotherapy. A randomized trial by the Medical Research Council Brain Tumour Working Party showed no benefit to PCV chemotherapy for newly diagnosed GBM.\textsuperscript{12} However, PCV has certain activity, especially for malignant glioma with oligodendroglial component.\textsuperscript{3,28} Therefore, this regimen may be important for recurrent GBM.

Cyclophosphamide is among the list of possible chemotherapies for recurrent GBM. However, the reference cited in the NCCN guideline is a report of recurrent anaplastic astrocytomas, and the efficacy of cyclophosphamide for recurrent GBM is not known.\textsuperscript{5} Lastly, platinum-based regimens are reported to show modest activities for recurrent GBM.\textsuperscript{1,27}

**On-going Phase 3 Trials for Future Revision of the Standard Therapy**

Table 3 shows four on-going randomized phase 3 confirmatory trials for GBM. Another schedule of TMZ administration (RTOG 0525), additive effect of bevacizumab (RTOG 0825, AVAglio), and also possible additive effect of cilengitide, integrin αvβ5 inhi-
In conclusion, the survival of patients with GBM continues to improve, albeit more slowly than we would like. Various new agents are currently under study, singly and in combination. Improved understanding of the complex biology of GBM may allow for more rational and effective therapy selection for patients, further extending survival in the years to come.

### References


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