Glioblastoma: Current Perspectives, Clinical Challenges, and Trends in Treatment

CME Learning Objectives
At the conclusion of this activity, participants should be able to:

• Understand use of temozolomide in management of newly diagnosed glioblastoma.
• Describe the applicability of molecular studies in glioblastoma case management.
• Evaluate investigational treatments for glioblastoma and the clinical trials examining their efficacy and safety.
Introduction

Glioblastoma is a rare and deadly disease that until recently had few effective therapeutic options. Concomitant with therapeutic improvements, comprehension of the complexity of this multi-faceted disease is increasing. Researchers are slowly finding numerous mechanisms at the molecular level that seem to be involved in glioblastoma’s progression and resistance to treatment. The National Comprehensive Cancer Network recommends that the best management for patients with cancer is participation in clinical trials. This is particularly apparent with glioblastoma. However, the rarity of the disease has placed constraints on performing large clinical trials. Some of these constraints were overcome when the Radiation Therapy Oncology Group (RTOG) successfully designed and performed an international phase 3 clinical trial, RTOG 0525, which examined more than 800 patients with newly diagnosed glioblastoma.

This monograph will review the results of the RTOG 0525 trial, in which a dose-intense schedule of temozolomide was compared to standard dose. Other treatment modalities that are currently being investigated, such as targeted agents and immunotherapy, are also discussed in this monograph. Expert commentary on these studies is provided in interviews with leading clinicians. Through analysis of clinical trials that are underway, this monograph will allow insight into the future for glioblastoma therapy.
Glioblastomas are notoriously difficult to manage, requiring coordinated efforts that frequently produce suboptimal results. In addition to treatment limitations, biological factors contribute to the challenge of developing effective treatment for glioblastomas. Studies suggest that this tumor, similar to other cancers, does not follow the traditional oncologic format of a repopulating tumor clonogen that undergoes accelerated repopulation after treatment. Instead, researchers believe that this cancer is driven by a subpopulation of cancer stem cells that is uniquely resistant to radiation and chemotherapy, and is capable of regrowing after these treatments.

Although treatment advances have been made, a significant majority of patients with glioblastoma succumb to the disease. Historically, conventional treatment for glioblastoma included surgical resection followed by radiation therapy. The value of this combined approach was supported by clinical trial data showing that the addition of radiotherapy prolonged survival to 9 months compared with 3 months with no treatment. However, both radiotherapy and surgery have limitations.

Radiotherapy

When undergoing radiotherapy, radiation injury can occur to normal brain tissue if the dosage exceeds treatment threshold dose. Newer techniques allow minimization of the dose delivered to normal brain tissue, focusing on enhancing the radiation dose to the tumor itself. Developing methods to further improve targeted delivery of radiation is another research opportunity.

Surgery

Advancements in surgical techniques have reduced postoperative complications. However, complete surgical resection of the tumor is difficult due to infiltration of tumor cells into the normal brain parenchyma in essentially all patients. Extent of resection has been associated with survival. For example, data from a retrospective analysis of 416 consecutive patients with glioblastoma revealed a survival advantage with resection of 98% or more of the tumor volume compared with patients with resections of less than 98% (median survival 13 months vs. 8.8 months; P < .0001). The current recommendations, therefore, are to achieve as extensive a resection as possible, while preserving neurologic function. The search for new surgical modalities that allow more accurate identification of the tumor at the time of surgery and more complete resection is also an ongoing area of research. For example, studies have shown that a significantly larger number of complete resections (defined as absence of contrast-enhancing tumor on early postoperative MRI) could be achieved using fluorescence-guided resections with 5-aminolevulinic acid (ALA)-induced tumor fluorescence compared with conventional microsurgery (65% vs. 36%, P < .001).

The primary prognostic tools during the era of treatment with surgery followed by radiotherapy were the primary prognostic tools during the era of treatment with surgery followed by radiotherapy. Over time, however, evidence has accumulated that demonstrates the impact of extent of resection on survival. A study of 416 consecutive patients with glioblastoma revealed a survival advantage with resection of 98% or more of the tumor volume compared with patients with resections of less than 98% (median survival 13 months vs. 8.8 months; P < .0001). The current recommendations, therefore, are to achieve as extensive a resection as possible, while preserving neurologic function. The search for new surgical modalities that allow more accurate identification of the tumor at the time of surgery and more complete resection is also an ongoing area of research. For example, studies have shown that a significantly larger number of complete resections (defined as absence of contrast-enhancing tumor on early postoperative MRI) could be achieved using fluorescence-guided resections with 5-aminolevulinic acid (ALA)-induced tumor fluorescence compared with conventional microsurgery (65% vs. 36%, P < .001).

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Continued on next page...
extent of surgical resection and use of adjuvant radiation. In the early 1990s, data from more than 1,500 patients in the Radiation Therapy Oncology Group (RTOG) radiation clinical trials were used to develop six recursive partitioning analysis (RPA) classes, which had been shown to have prognostic significance. Prognostic factors included age, histology, mental status, Karnofsky performance status (KPS), symptom duration, extent of surgery, neurological class, and radiation therapy dose. RPA class has become a standard stratification variable in glioblastoma randomized controlled trials, providing important baseline balance among treatment groups.

Chemotherapy

Research efforts to develop effective chemotherapy were largely unsuccessful until recently. Agents were not active in the disease, or those that showed activity were prevented from having adequate penetration into and around the tumor by the blood-brain barrier. Although the blood-brain barrier may be compromised in the immediate vicinity of the tumor where microscopic penetration of the disease into normal brain parenchyma occurs, the intact blood-brain barrier allows a significant compartment of the tumor to go unchallenged by chemotherapy.

Current Standard of Care for Newly Diagnosed Glioblastoma

In 2005, researchers reported results from the landmark study of the oral alkylating agent temozolomide, performed by the European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group. In that study, 573 patients with newly diagnosed glioblastoma were randomly assigned to receive radiotherapy with or without continuous daily temozolomide (75 mg/m² of body surface area) throughout radiotherapy followed by 6 cycles of adjuvant temozolomide (150 to 200 mg/m² for 5 days of each 28-day cycle). At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio (HR) for death in patients receiving radiotherapy plus temozolomide was 0.63 (95% confidence interval [CI], 0.52-0.75; P < .001). Five-year follow-up data supported the significant survival advantage conferred by the addition of temozolomide to radiotherapy, with an overall survival of 9.8% in patients treated with temozolomide compared with 1.9% in patients treated with radiotherapy alone (P < .0001).

These survival data resulted in the adoption of this regimen as the glioblastoma standard of care. In Europe and Canada this adjuvant therapy continues to be provided for 6 cycles, while many centers in the United States continue treatment for 12 cycles. This advancement marked the entry of a chemotherapeutic agent into routine glioblastoma management.

Safety profile of temozolomide

Temozolomide is a well-tolerated medication. In the initial study of the temozolomide regimen, toxic effects were reported as the reason for discontinuation of therapy in 5% and 8% of patients during concomitant temozolomide/radiotherapy and adjuvant therapy periods, respectively. The most common side effects from temozolomide are fatigue and constipation. Rarely, myelotoxicity or a reduction in blood counts can occur.

Being able to predict the small number of patients who may have myelotoxicity is an important objective because although myelotoxicity is rare, when it does occur, it can be clinically significant and cause treatment delays. In addition to clinical factors such as age and sex, molecular screening of single nucleotide polymorphisms (SNPs) and O6-methylguanine-DNA methyltransferase (MGMT) enzyme activity in peripheral blood mononuclear cells is being explored as a possible method to determine patients at risk for myelotoxicity, and for whom therapy should be altered.

References


Full references are available at www.healio.com/hematology-oncology/education-lab.
RTOG 0525: Examining the Effects of Dose Intensification on Survival

Notwithstanding the undeniable progress made in recent years in the treatment of glioblastoma, developing improved treatment regimens that will further increase patient survival is an ongoing challenge. Building on previous results, the Radiation Therapy Oncology Group (RTOG) conducted a major randomized controlled trial of management strategies in newly diagnosed glioblastoma to determine the effect of dose-dense postradiation temozolomide. The primary objective of this study, RTOG 0525, was to determine if dose-intensifying the postradiation temozolomide component of a chemoradiation regimen (extending treatment from 5 days to 21 days during each 28-day cycle) improved overall survival (OS). Secondary objectives included assessment of 1) the effect of the dose-intense temozolomide on progression-free survival (PFS); 2) the effect of dose-intense temozolomide on both OS and PFS in patient subgroups based on O6-methylguanine-DNA methyltransferase (MGMT) methylation status; 3) toxicity profiles; and 4) symptom burden, neurocognitive function, and health-related quality of life.

Results of this trial were presented at the American Society of Clinical Oncology (ASCO) 2011 Annual Meeting in Chicago, IL. This RTOG study was an open-label, collaborative trial between the RTOG, the European Organisation for Research and Treatment of Cancer (EORTC), and the North Central Cancer Treatment Group (NCCTG). Sample size determination was based on achieving an improvement in median OS from 14 months to 17.6 months, equivalent to a hazard ratio of 0.87. A total of 750 randomized patients were required to achieve 80% power of detecting the expected difference in OS with 4 interim and 1 final analyses, with a one-sided type 1 error of 2.5%.

Participants were required to have a centrally confirmed diagnosis of glioblastoma or gliosarcoma based on World Health Organization (WHO) grade IV criteria with no other recent malignancy and adequate hematologic, renal, and hepatic function. They also were to consent to submission of their tissue. The tumor was required to have a supratentorial component. Participants were required to be neurologically stable with adequate tissue for prospective MGMT analysis. Eligibility criteria also included age >18 years, Karnofsky performance status (KPS) ≥60%, tissue block with ≥1 cm² tumor, and recursive partitioning analysis (RPA) class III, IV, or V (class VI was excluded).

Considering possible exclusions, an accrual goal of 1,153 patients was established. Between January 2006 and June 2008, 1,173 patients were accrued and assessed for eligibility. Of these, 1,125 were suitable for randomization. Eight hundred thirty-three patients were randomized from the total 1,173 accrued. There were no significant demographic or clinical differences between the 2 groups at baseline. Both groups received the standard concomitant radiotherapy and temozolomide for 6 weeks prior to randomization. Patients randomized to the standard-dose group (n = 411), received 150 mg/m² to 200 mg/m² temozolomide on days 1 through 5 of a 28-day cycle. Group 2, the dose-intense group (n = 422), received 75 mg/m² to 100 mg/m² temozolomide on days 1 through 21 of a 28-day cycle. Patients in both groups were given 6 to a maximum of 12 cycles of adjuvant radiotherapy. Patients were stratified according to 3 factors: 1) RPA class (III, IV, or V); 2) MGMT methylation (methylated, unmethylated, or not determined); and 3) radiation type (European vs. United States).

Results of this trial were presented at the 2011 ASCO Annual Meeting by Mark R. Gilbert, MD, of the MD Anderson Cancer Center in Houston, TX. There was no statistically significant difference between the 2 treatment arms in terms of median OS (16.6 months vs. 14.9 months; P = .63) median PFS (5.5 months vs. 6.7 months; P = .06), or methylation status. However, MGMT methylation was associated with improved OS (21.2 months vs. 14 months; P < .0001). PFS (8.7 months vs. 5.7 months; P < .0001) and response (P = .012). Cox modeling showed that MGMT status and RPA class were significant predictors of OS while the treatment arm and radiation technique (EORTC vs. RTOG) were not.
Both treatment arms were well-tolerated, and the majority of patients either completed therapy or stopped because of progressive disease, not because of treatment-related toxicity. However, during the postradiation phase, there was a statistically significant increase in grade 3, grade 4, and grade 5 toxicity in the dose-intense treatment group compared with the group on standard treatment (194 vs. 120; \( P < .0001 \)). Most of the difference was due to lymphopenia (107 vs. 51) and fatigue (33 vs. 12; Table 3, page 8). Despite the incidence of lymphopenia, there was not an increase in opportunistic infections in the dose-intense group compared with the standard-dose group.

**Molecular Markers Substudy**

In a substudy of RTOG 0525, a set of molecular markers in glioblastoma was evaluated. The rationale for the study was that there are variations in outcomes among patients with newly diagnosed glioblastoma that are not well-explained, and although survival markers for glioblastoma exist, they currently do not have a major impact on clinical practice. In this study, molecular biomarkers were combined into a single panel, and it was assessed whether the combination had a greater impact compared with single-marker analysis. Results of this substudy were also presented at the 2011 ASCO Annual Meeting by Kenneth D. Aldape, MD, of the MD Anderson Cancer Center in Houston, TX.

Four types of biomarkers were assessed in this study, namely the isocitrate dehydrogenase 1 (IDH1) mutation, the CpG island methylator phenotype, MGMT methylation, and a new version of an mRNA predictor that was developed for this study. This biomarker panel was tested on a training set of retrospectively collected samples at the MD Anderson Cancer Center. A statistical model was developed and then applied to samples from the RTOG 0525 trial.

The mRNA panel was validated on a prior 9-gene set, verifying that this panel is, in fact, prognostic. After the development of this 9-gene set, additional microarray data became available from the Cancer Genome Atlas as well as other sources. With this additional data, a list of 384 survival genes was identified. Real-time PCR assays for these genes were performed on archival formalin-fixed paraffin-embedded glioblastoma samples. This led researchers to pare down to a 19-gene list (Table 4, page 9), 16 of which were overexpressed in
unfavorable survivors, and 3 were expressed in favorable survivors. Seven genes from the previous 9-gene list were included; 5 were overexpressed in unfavorable survivors, 2 were overexpressed in favorable survivors.

The MGMT assay was revised for this study. Twenty-two methylation-specific PCR assays (MSPs) were designed along the CpG island of the MGMT regulatory region and used to test a set of samples from MD Anderson. From this a set of MGMT assays that appeared prognostic were developed.4

The CpG island methylator phenotype (CIMP) is a concordant methylation of a defined set of CpG sites. This phenotype is common in lower-grade gliomas, but also occurs in 5% to 10% of glioblastomas, and is associated with improved prognosis.6 Data from the training set suggested that tumors could be divided into 3 groups based on the CIMP phenotype: CIMP-negative, CIMP-intermediate, and CIMP-positive.4 CIMP-positive tumors are concordant with IDH1 mutations, but there are exceptions.6 Therefore, both CIMP and IDH1 biomarkers were investigated in this study.4

This panel of biomarkers was applied to 254 samples from a retrospectively collected archive at MD Anderson. Results demonstrated that patients with the IDH1 mutation were associated with favorable prognosis, as previously demonstrated. Patients could be divided into 3 groups based on CIMP phenotype: CIMP-negative patients were associated with poor prognosis, CIMP-positive patients with good prognosis, and CIMP-intermediate patients with intermediate prognosis. Patients could also be divided into 3 survival groups based on MGMT status (favorable, intermediate, and unfavorable). With regard to the mRNA panel, mRNA scores were consolidated into 4 survival groups. Good survival discrimination was observed between the 2 groups with favorable patient outcomes and the 2 groups with unfavorable patient outcomes.4

These 4 biomarkers were combined into a single panel.4 Each biomarker had 2, 3, or 4 possible outcomes. Thus there were 72 possible biomarker combinations that any given sample could have. These combinations were consolidated into 4 survival groups by recursive partitioning analysis. The most favorable survival group had a very positive outcome compared with the other 3 less favorable survival groups. The 4-biomarker set demonstrated improved survival association as compared with any of the single biomarkers.

The rules defined by the test set were applied to an independent validation set, which were samples from MD Anderson. Results demonstrated that patients with the IDH1 mutation were associated with favorable prognosis, as previously demonstrated. Patients could be divided into 3 survival groups based on MGMT status (favorable, intermediate, and unfavorable). With regard to the mRNA panel, mRNA scores were consolidated into 4 survival groups. Good survival discrimination was observed between the 2 groups with favorable patient outcomes and the 2 groups with unfavorable patient outcomes.4

Table 1. RTOG 0525: Baseline Demographic and Clinical Characteristics

<table>
<thead>
<tr>
<th>Category</th>
<th>Group 1 (standard dose)</th>
<th>Group 2 (dose-intense)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50</td>
<td>112 (27%)</td>
<td>111 (26%)</td>
</tr>
<tr>
<td>≥50</td>
<td>299 (73%)</td>
<td>311 (74%)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>239 (58%)</td>
<td>237 (56%)</td>
</tr>
<tr>
<td>Female</td>
<td>172 (42%)</td>
<td>185 (44%)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>319 (78%)</td>
<td>328 (78%)</td>
</tr>
<tr>
<td>Non-white</td>
<td>13 (3%)</td>
<td>15 (3%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>79 (19%)</td>
<td>79 (19%)</td>
</tr>
<tr>
<td>KPS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60-80</td>
<td>138 (34%)</td>
<td>146 (35%)</td>
</tr>
<tr>
<td>90-100</td>
<td>273 (66%)</td>
<td>276 (65%)</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>14 (3%)</td>
<td>13 (3%)</td>
</tr>
<tr>
<td>Partial resection</td>
<td>167 (41%)</td>
<td>188 (45%)</td>
</tr>
<tr>
<td>Total resection</td>
<td>230 (56%)</td>
<td>221 (52%)</td>
</tr>
<tr>
<td>Radiation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RTOG/NCCTG</td>
<td>337 (82%)</td>
<td>349 (83%)</td>
</tr>
<tr>
<td>EORTC</td>
<td>74 (18%)</td>
<td>73 (17%)</td>
</tr>
<tr>
<td>Neurologic Function</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No symptoms</td>
<td>140 (34%)</td>
<td>147 (35%)</td>
</tr>
<tr>
<td>Minor symptoms</td>
<td>186 (45%)</td>
<td>196 (45%)</td>
</tr>
<tr>
<td>Moderate symptoms</td>
<td>84 (20%)</td>
<td>75 (18%)</td>
</tr>
<tr>
<td>Severe symptoms</td>
<td>2 (1%)</td>
<td>4 (1%)</td>
</tr>
<tr>
<td>MGMT Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Methylated</td>
<td>122 (30%)</td>
<td>123 (29%)</td>
</tr>
<tr>
<td>Unmethylated</td>
<td>254 (62%)</td>
<td>263 (62%)</td>
</tr>
<tr>
<td>Unknown</td>
<td>35 (8%)</td>
<td>36 (9%)</td>
</tr>
<tr>
<td>RPA Class</td>
<td></td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>85 (21%)</td>
<td>86 (20%)</td>
</tr>
<tr>
<td>IV</td>
<td>251 (61%)</td>
<td>259 (61%)</td>
</tr>
<tr>
<td>V</td>
<td>75 (18%)</td>
<td>77 (19%)</td>
</tr>
</tbody>
</table>

KEY: EORTC — European Organisation for Research and Treatment of Cancer; KPS — Karnofsky performance status; MGMT — O-6-methylguanine-DNA methyltransferase; NCCTG — North Central Cancer Treatment Group; RPA — recursive partitioning analysis; RTOG — Radiation Therapy Oncology Group

the 833 patients enrolled in the RTOG 0525 trial. Additionally, 48 patients who registered for the trial but were deemed ineligible due to tumor progression prior to randomization were included in this analysis because their survival time was still tracked. All 4 biomarkers were obtained in 725 of these 881 patients (82%). This population was representative of all 3 collaborative groups of RTOG 0525 (RTOG, EORTC, and NCCTG). The combined molecular predictor from the training set had a favorable survival discrimination compared with any single biomarker. This molecular predictor was shown to be independent of relevant clinical variables through multivariate analysis (Table 5).4

When the molecular predictor was combined with RPA class to generate a molecular-clinical predictor, enhanced survival discrimination among subgroups was

<table>
<thead>
<tr>
<th>Table 2. Survival on Standard Adjuvant Temozolomide (Group 1) vs. Dose-intense Temozolomide (Group 2)*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Group</strong></td>
</tr>
<tr>
<td>All eligible</td>
</tr>
<tr>
<td>All randomized Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>MGMT Methylated</td>
</tr>
<tr>
<td>Unmethylated</td>
</tr>
<tr>
<td>Methylated Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
<tr>
<td>Unmethylated Group 1</td>
</tr>
<tr>
<td>Group 2</td>
</tr>
</tbody>
</table>

*Outcomes data from study registration
MGMT — O-6-methylguanine-DNA methyltransferase

<table>
<thead>
<tr>
<th>Table 3. Treatment-Related Adverse Events: Adjuvant Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Category</strong></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Anemia*</td>
</tr>
<tr>
<td>Leukopenia</td>
</tr>
<tr>
<td>Neutropenia</td>
</tr>
<tr>
<td>Lymphopenia</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Fatigue</td>
</tr>
<tr>
<td>Nausea/vomiting</td>
</tr>
</tbody>
</table>

*1 Grade 5 toxicity in Arm 1
Group 1 — Standard dose; Group 2 — Dose-intense
observed. When analyzed by treatment arms, the molecular clinical predictor demonstrated good survival discrimination in both groups, with no difference between the 2 treatment arms.4 The molecular-clinical predictor represents a possible stratification factor for future clinical trials that is analogous to the clinical RPA as currently used. This predictor also represents a possible prognostic marker that could be considered in the management of patients with glioblastoma.4

Strengths and Limitations of Substudy

The strengths of the molecular biomarkers substudy included large sample size (nearly 1,000 samples). Moreover, the use of a training set to develop a model which was then applied and validated in clinical trial samples is considered statistically robust. Furthermore, these assays can be applied to formalin-fixed paraffin-embedded samples, which means they can be used in many patients with glioblastoma. Importantly, this study demonstrated the feasibility of obtaining molecular correlates in a cooperative group setting.4 There were also limitations to this study, one being that patients with needle biopsies were not included, so it is not known whether the molecular-clinical predictor can be applied to these patients. Also, these biomarkers require molecular techniques that may be beyond the scope of some pathology departments. Finally, although the RTOG 0525 tissue was collected prospectively, the markers were obtained retrospectively and therefore require validation.4

Net Clinical Benefits Substudy

The RTOG 0525 protocol included an important substudy entitled, “Net Clinical Benefits.”7 Patients in this substudy underwent longitudinal testing of several modalities including symptom assessment, neurocognitive function, and health-related quality of life (HRQOL). The study design included validated reliable instruments for assessing these 3 components.

Symptom assessment used the 28-item MD Anderson Symptom Inventory Brain Tumor Module (MDASI-BT), which includes 13 core MDASI symptom severity items, 6 core MDASI symptom interference items, and 9 brain tumor-specific symptom items (weakness on 1 side of the body, difficulty understanding, difficulty speaking, seizures, difficulty concentrating, vision, change in appearance, change in bowel pattern [diarrhea or constipation], and irritability). An MDASI User’s Guide is available from the MD Anderson Symptom Research website, which addresses FDA requirements for the use of patient-reported outcomes in clinical trials.8

Neurocognitive function was measured by 3 widely used objective tests, which have been included in several RTOG studies to assess cognitive function. The Trail-making Test requires the subject to connect the dots between numbers or numbers and letters as quickly as possible, and evaluates visual attention and task switching.9 The Controlled Oral Word Association Test (COWAT) measures phonemic verbal fluency, where patients make verbal associations to 3 specified letters in trials of 1 minute each.10 As its name suggests, the Hopkins Verbal Learning Test assesses learning and memory, and includes words learned, retention, and recognition discrimination.11

Table 4. 19-Gene mRNA List

<table>
<thead>
<tr>
<th>Overexpressed in Unfavorable Survivors</th>
<th>Overexpressed in Favorable Survivors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• SOD2</td>
<td>• KCND2</td>
</tr>
<tr>
<td>• TIMP1</td>
<td>• OLIG2</td>
</tr>
<tr>
<td>• TNC</td>
<td>• RTN1</td>
</tr>
<tr>
<td>• VEGFA</td>
<td>• CHI3L1</td>
</tr>
<tr>
<td>• CHI3L1</td>
<td>• EMP3</td>
</tr>
<tr>
<td>• EMP3</td>
<td>• SPP1</td>
</tr>
<tr>
<td>• SPP1</td>
<td>• C1S</td>
</tr>
<tr>
<td>• C1S</td>
<td>• ANXA1</td>
</tr>
<tr>
<td>• ANXA1</td>
<td>• CLIC1</td>
</tr>
<tr>
<td>• CLIC1</td>
<td>• COL1A2</td>
</tr>
<tr>
<td>• COL1A2</td>
<td>• GPNMB</td>
</tr>
<tr>
<td>• GPNMB</td>
<td>• IGFBP2</td>
</tr>
<tr>
<td>• IGFBP2</td>
<td>• ITGB2</td>
</tr>
<tr>
<td>• ITGB2</td>
<td>• PCOLCE</td>
</tr>
<tr>
<td>• PCOLCE</td>
<td>• PDPN</td>
</tr>
</tbody>
</table>

Underlined genes indicate those from the 9-gene list that was used to validate the mRNA panel in the molecular markers substudy.


Table 5. Multivariate Analysis: Molecular Predictor is Independently Associated with Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Training set</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP4 v. MP1</td>
<td>10.4</td>
<td>4.93-22.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RPA V v. III</td>
<td>1.21</td>
<td>0.68-2.11</td>
<td>0.6621</td>
</tr>
<tr>
<td>Validation set (RTOG 0525)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MP4 v. MP1</td>
<td>3.92</td>
<td>1.75-10.51</td>
<td>0.0004</td>
</tr>
<tr>
<td>RPA V v. III</td>
<td>2.22</td>
<td>1.55-3.16</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

QOL testing was performed with the EORTC QLQ-C30 and the Brain Cancer Module (BN20). The former is a 30-item questionnaire, while the latter is 20 questions pertaining to HRQOL in patients with brain cancer.12,13

For this study, a subset of patients completed surveys at baseline and longitudinally while on treatment.7 Univariate and multivariate modeling was used to determine the prognostic value of changes in protocol-defined baseline measurements at cycle 1 for OS and PFS. Differences in symptomatic worsening between groups were compared from baseline to cycle 4 in patients without progression. Results of this substudy were presented at the 2011 ASCO Annual Meeting by Terri S. Armstrong, PhD, ANP-BC, FAANP of the MD Anderson Cancer Center in Houston, TX. Neurocognitive function tests and the physical functioning QOL scale were associated with both OS and PFS at baseline. Changes from baseline to cycle 1 were associated with OS and PFS for all measures. The MDASI-BT and global QOL detected symptom differences between the arms from baseline to cycle 4, with the dose-intense group experiencing more symptoms. The authors of this study concluded that longitudinal collection of net clinical benefit data is feasible and complementary in cooperative group studies, providing an added dimension to standard outcome measures.7 These measures may impact patient stratification, help to assess response or progression, and help in risk/benefit analyses.7

Implications

Although RTOG 0525 did not demonstrate improved efficacy for dose-dense temozolomide for newly diagnosed glioblastoma regardless of methylation status, it was monumental in several aspects. This trial underscored the feasibility of performing a large-scale randomized clinical trial in an international collaboration.3 Furthermore, the study showed that tumor collection and analysis for stratification and additional correlative studies is possible.4 Also, the prognostic significance of MGMT methylation status in glioblastoma was confirmed.5 Measures of symptom burden, neurocognitive function, and HRQOL were successfully incorporated into this trial and demonstrated between-arm differences and an impact on prognosis.7 RTOG 0525 provides a platform for future studies, integrating tumor and patient factors to optimize individual treatment.

References


Full references are available at www.healio.com/hematology-oncology/education-lab.
Applying Lessons from RTOG 0525 to Clinical Practice and Research

An interview with David A. Reardon, MD

Were you surprised by the negative results of RTOG 0525?

David A. Reardon, MD: Yes, I was surprised. The study had a sound rationale, supported by preclinical data. I was not expecting a dramatic improvement, but I did think there would at least be some modest benefit.

Do you think that the outcome could be the result of the trial design or the dosing scheme involved?

Reardon: I believe that the dosing scheme was a reasonable choice. Various dosing schedules with temozolomide have been studied and the dosing schedule used in RTOG 0525 (ie, 75 mg/m² to 100 mg/m² temozolomide on days 1 through 21 of a 28-day cycle) was a reasonable attempt at dose intensification. I think that any further intensification would lead to issues with toxicity and adverse events.

Is it worthwhile to explore other dosing schedules?

Reardon: I do not feel there is justification for exploring alternative schedules. I think that this dosing schedule was similar enough to the degree of intensification associated with other dose-dense schedules that any other changes would probably not result in a difference. I do think that altering the dosing schedule so that another agent with synergistic anti-tumor activity could be administered concurrently may lead to a benefit. For example, there are preclinical data suggesting that irinotecan, a topoisomerase inhibitor, will have a synergistic anti-tumor effect when combined with an alkylator such as temozolomide. So potentially, if the dose of temozolomide was increased to result in high levels of alkylated tumor DNA, a synergistic effect is more likely to be achieved in combination with another agent, as opposed to an additive effect that may be observed at a lower dose. These types of possibilities are reasonable to pursue if there is a biological, preclinical rationale.

Another possibility is high-dose therapy and stem cell rescue, where higher doses are administered and normal bone marrow is removed and reconstituted with harvested autologous peripheral blood stem cells.

Regarding the substudy of the biomarker panel, can you discuss the potential impact of this type of analysis on the management of glioblastoma and potentially other forms of cancer?

Reardon: The approach that was taken in this substudy was quite comprehensive. I think that a centralized facility or laboratory is required to be able to execute these types of studies, not because they are technically challenging, but because they should be performed consistently. If there were 100 different laboratories from different parts of the country involved in the same study, there would most likely be variations in collection and analysis methods that could potentially impact the results. Therefore, I think the broad applicability of these types of studies is somewhat limited at this point.

On the other hand, I think that this substudy did provide intriguing insight into the different outcomes observed for patients and why there may be such a spectrum of outcomes. MGMT methylation status is known to be a contributor to these various outcomes, but I think there are more contributing factors. This substudy was a significant step to providing insight into what some of these possibilities may be.

Could this type of biomarker panel be used to stratify likely responders and affect future clinical trial design?

Reardon: Absolutely. These results must first be validated prospectively, not just in RTOG 0525, but also in another large prospective data set (eg, another randomized study that is moving forward). Once they are validated, it will be important for subsequent studies to stratify and equally distribute patients based on these factors. The clinical version of this, which was developed from the recursive partitioning analysis performed by the RTOG 20 years ago and then more recently confirmed in the modern temozolomide era, demonstrated the importance of clinical prognostic factors (ie, age, degree of resection, KPS, etc). As a result, ongoing clinical trials are stratifying enrollment on different arms so that they are equally weighted by these important clinical prognostic factors. The same approach should be implemented with regard to the molecular prognostic factors, because if it is not, different treatment arms may be weighted differently in a favorable subgroup of patients based on these markers. This may influence the outcome and researchers may be deceived into thinking a treatment is successful or unsuccessful when in...
Do you think it is possible to take the biomarker panels used in this substudy and revisit previous negative trials to identify subsets of patients who might benefit from treatments that had been considered unsuccessful?

Reardon: Yes, but it will depend on what is available in terms of tumor material from those studies. One of the key features of RTOG 0525 that I think has been underemphasized is the comprehensive way that tissue was secured for so many patients. Enrollment was contingent on having tumor material available for analysis. This was a major effort, and many thought that it would not be possible. RTOG 0525 was the first study to demonstrate that in a large multinational effort, tumor material availability could be mandated and successfully collected.

I think that from prior negative studies, there would be a subset of patients who would have adequate material available for analysis. As long as these patients seem representative of the enrolled patient population, it may be worthwhile to analyze the tumor material and determine whether there were important differences in the outcome based on the marker profiles.

Could this type of analysis be eventually translated into clinical or hospital practice, or do the costs and time involved render it to only be a consideration in large scale trials?

Reardon: I think that for the time being it is the latter. However, technology is advancing and constantly evolving. For example, MGMT methylation analysis is now routinely available in commercially available assays. The IDH1 mutation analysis that was part of the biomarker panel is straightforward with widespread applicability. So certainly with time, this biomarker panel could be readily available.

What are the next steps needed to make greater use of this type of analysis?

Reardon: I think that it should be validated in another prospective cohort of patients and it must be a large data set in order to be robust enough to confirm the RTOG 0525 substudy results. Some possibilities are RTOG 0825, the RTOG study that is about to launch, or one of the EORTC studies.

In terms of the Net Clinical Benefits substudy, how useful would this type of patient self-reporting and other issues be in guiding treatment?

Reardon: I think that in general we all advocate for priority on quality of life and assessment of it for any of the treatments being implemented. Glioblastoma is a disease with a life expectancy of slightly longer than 1 year. Therefore, quality of life is a critical consideration for these patients. I believe that the tools for assessing quality of life are improving; they are becoming more user-friendly and less cumbersome. In this patient population, assessing patient-reported outcomes is complicated because there are many confounding factors independent of the tumor that could influence these outcomes (eg, seizures, concurrent medications, depression, neuro-psychiatric issues).

Nonetheless, patient-reported outcomes are certainly valuable tools that are useful for monitoring overall outcomes. In a whole cohort of patients, confounding factors tend to “wash out” with a sufficient number of patients involved, providing a level of reassurance about the preservation of quality of life. On the other hand, utilization of the data on a smaller scale can be difficult because of the number of confounding variables.

Do you think this type of patient self-reporting would be useful in designing clinical trials in the future?

Reardon: Yes. I think that this type of data is easy to collect and it is worthwhile to do so. Patients should not be subjected to treatment that results in a deterioration of quality of life if the treatment only provides 4 to 6 weeks of added survival.

Are these results likely to have a significant impact in managing patients with glioblastoma?

Reardon: I think that they will raise awareness of the importance of integrating this analysis on a regular basis as clinical trials go forward. On the other hand, there are limitations associated with this type of analysis and I think having more of this data available heightens awareness of that aspect. This awareness can motivate clinicians and researchers to develop more effective tools and strategies to improve on the assessment of quality of life.

Do you have any recommendations for clinicians who are considering implementation of this type of patient reporting in their practice?

Reardon: I think that there are validated useful tools that are currently available and I would certainly use them. I think that it is reasonable to model their implementation based on how they were utilized in RTOG 0525, so that there is consistency and results can be compared from one study to another. Otherwise it would be difficult to interpret the data relative to other therapies.

Reference

Targeted Therapies and Immunotherapies in Glioblastoma

In addition to alterations in the dosing schedule for standard therapy, a variety of other treatment strategies to improve survival in newly diagnosed glioblastoma are being investigated. These strategies include the use of monoclonal antibodies, vaccines, immunostimulants, and targeted therapies.

Immunotherapy

The cytolytic power of the immune system can be harnessed to destroy cells that express “non-self” antigens on their surfaces; this effect is observed in the rejection of foreign tissue following organ transplantation. The goal of immunotherapy in the treatment of cancer is to manipulate the immune system to recognize the “non-self” antigens that are expressed in tumor cells. There are a variety of approaches through which this may be accomplished.

Monoclonal antibodies

Monoclonal antibodies are a form of immunotherapy that is being evaluated in the management of various cancers. Bevacizumab, a humanized monoclonal antibody that targets vascular endothelial growth factor (VEGF), has been shown to improve patient outcomes in combination with chemotherapy (most commonly irinotecan) in recurrent glioblastoma, and positive results in 2 prospective phase 2 studies led to accelerated approval by the US Food and Drug Administration (FDA) for bevacizumab as a single agent in recurrent glioblastoma. The efficacy and safety of bevacizumab in patients with newly diagnosed glioblastoma is currently being investigated. A phase 2 study has shown that adding bevacizumab to radiation therapy and temozolomide followed by bevacizumab, irinotecan, and temozolomide for the treatment of newly diagnosed glioblastoma has moderate toxicity and may improve efficacy compared with historical controls. In another phase 2 study, it was demonstrated that patients treated with bevacizumab and temozolomide during and after radiation therapy showed improved progression-free survival (PFS) without improved overall survival (OS) compared with the University of California, Los Angeles/Kaiser Permanente Los Angeles (KPLA) control group. Two recently completed phase 3 trials investigated whether adding bevacizumab to standard therapy will improve outcomes in patients with newly diagnosed glioblastoma. Results are awaited.

Other antibodies in addition to bevacizumab are being investigated for the treatment of newly diagnosed glioblastoma. Nimotuzumab, an anti-epidermal growth factor receptor (EGFR) monoclonal antibody, has been examined for the treatment of newly diagnosed glioblastoma in another phase 3 trial. This trial compared nimotuzumab in addition to standard radiation and chemotherapy with temozolomide (Arm A) to standard radiation and temozolomide (Arm B). Twelve-month PFS was 25.5% in arm A vs. 20.3% in arm B (P = .78). OS was 679 days in arm A vs. 596 days in arm B. For non-methylated O6-methylguanine-DNA methyltransferase (MGMT), the difference was most notable: OS was 19.6 months in arm A vs. 15.0 months in arm B. Thus no significant differences were observed between treatment arms.

Vaccines in the treatment of glioblastoma

Cancer vaccines are also being investigated in the treatment of glioblastoma. One such vaccine approach being investigated for the treatment of glioblastoma utilizes dendritic cells, which are considered to be the most potent type of antigen-presenting cells. In this approach, dendritic cells are cocultured with autologous tumor lysate to immunologically target endogenous tumor antigens. Initial studies of dendritic cell-based vaccine therapy for glioblastoma have shown acceptable toxicity and safety profiles. Multi-center randomized phase 2 and phase 3 trials investigating this approach to glioblastoma are currently underway. A phase 3 trial is currently underway. Other peptides are being investigated as cancer vaccine candidates as well. For example, in a phase 1 trial, personalized vaccination with peptides selected from 14 kinds of human leukocyte antigen (HLA)-A24-restricted peptide candidates based on pre-existing humoral immunity in patients with recurrent or progressive glioblastoma.
was studied. This trial demonstrated that the vaccine induced dose-dependent immune boosting, was well-tolerated, and no serious adverse drug reactions were encountered. Another approach to cancer vaccination is the use of autologous whole tumor cells. Vaccination of 19 patients with irradiated autologous whole tumor cells by using granulocyte-macrophage colony-stimulating factor as an adjuvant has been shown to induce a cell-mediated immune response, which appeared to be tumor-specific. Seventeen patients developed a delayed-type hypersensitivity (DTH) response to vaccination that appeared to be directed against the autologous tumor. In 8 patients there was radiological evidence of a response and in 5 patients there was evidence of clinical improvement. Median survival was 12 months (range 6 to 28 months), and both the presence of a DTH response and the radiological response correlated with survival ($P < .02$ and $P < .04$, respectively).

This strategy was also utilized in the development of a transforming growth factor (TGF)-$\beta$ antisense-modified tumor cell vaccine. Elevated levels of TGF-$\beta$ in patients with glioblastoma are associated with immunosuppression. Thus reducing levels of TGF-$\beta$ may improve the patient’s immune response to the tumor. A phase 1 clinical trial assessed the safety of a whole-cell vaccine comprising autologous tumor cells genetically modified by a TGF-$\beta_2$ antisense vector. Results of this clinical trial demonstrated that TGF-$\beta_2$ secretion by the tumor cells used to vaccinate patients was inhibited by 53% to 98%. The overall median survival was 68 weeks. Median survival of the responding patients was 78 weeks, compared with a historical median survival of 47 weeks for patients with glioma who received conventional treatment. The treatment was well-tolerated, with only low-grade transient treatment-related toxicities reported.

### Immunostimulants

Stimulating the immune system is yet another strategy being investigated in the treatment of glioblastoma. Polyinosinic-polycytidylic acid stabilized with poly-L-lysine and carboxymethylcellulose (poly-ICLC) is a synthetic double-stranded ribonucleic acid (dsRNA) viral mimic or pathogen associated molecular pattern (PAMP) that activates multiple elements of innate and adaptive immunity. Results of a phase 2 study suggest that when combined with standard radiation and concurrent temozolomide, poly-ICLC may improve survival. Common treatment-related adverse events included neutropenia, leukopenia, thrombocytopenia, and rash. In another phase 2 study, patients were treated with radiation therapy in combination with poly-ICLC followed by poly-ICLC as a single agent in 31 patients. The combined therapy appeared to be well-tolerated. The estimated 6-month PFS was 30% and the estimated 1-year PFS was 5%. Median time to progression was 18 weeks. The 1-year survival was 69% and the median survival was 65 weeks. This study suggests a survival advantage compared with historical studies using radiotherapy without chemotherapy, but no survival advantage compared with radiotherapy with adjuvant nitrosourea or non-temozolomide chemotherapy.

### Targeted Therapy

Targeted therapy represents another mode of treatment for glioblastoma. There are 30 classes of targeted agents being studied in the field of oncology. Many of these classes have multiple agents within them. Several of these agents are being investigated for the treatment of glioblastoma.

Integrins are a family of transmembrane receptor proteins. Many integrins bind their ligands through a short arginine-glycine-aspartate (RGD) amino acid sequence that comprises the cell attachment site for many proteins.

### Table. Survival Comparison: NABTTCC/UCSF Data

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient Number (N)</th>
<th>Survival</th>
<th>Median (months)</th>
<th>6-month</th>
<th>12-month</th>
<th>18-month</th>
<th>24-month</th>
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<tr>
<td>Historical NABTTCC non-TMZ</td>
<td>217</td>
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<td>12.0</td>
<td>78%</td>
<td>49%</td>
<td>22%</td>
<td>8%</td>
</tr>
<tr>
<td>EORTC RT+TMZ</td>
<td>287</td>
<td></td>
<td>14.6</td>
<td>86%</td>
<td>61%</td>
<td>39%</td>
<td>27%</td>
</tr>
<tr>
<td>NABTTCC RT+TMZ</td>
<td>49</td>
<td></td>
<td>16.2</td>
<td>88%</td>
<td>65%</td>
<td>41%</td>
<td>20%</td>
</tr>
<tr>
<td>NABTTCC RT+TMZ+new agent</td>
<td>244</td>
<td></td>
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<td>94%</td>
<td>81%</td>
<td>55%</td>
<td>37%</td>
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<tr>
<td>UCSF RT+TMZ+new agent</td>
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<td></td>
<td>19.5</td>
<td>94%</td>
<td>76%</td>
<td>NS</td>
<td>NS</td>
</tr>
</tbody>
</table>

Key: NABTTCC — New Approaches to Brain Tumor Therapy CNS Consortium; TMZ — temozolomide; RT — radiotherapy

These molecules fulfill signaling functions that are essential for cell migration, proliferation, survival, and adhesion to the extracellular matrix. These activities provide the basis for their critical role in angiogenesis, and integrins have been referred to as a “functional hub” for this process. Integrins are expressed in all cell types that are involved in angiogenesis, including many tumors.

The involvement of integrins in several aspects of the survival and progression of different cancers provides a rational basis for developing integrin-targeted therapeutic agents. Anti-integrin compounds have been under development for several indications, and 4 are currently approved for non-cancer indications. Three types of anti-integrin compounds are being evaluated in preclinical or clinical cancer trials: peptidomimetics, antibodies, and small organic molecules.

Cilengitide is currently the lead prototype in the RGD peptidomimetic category of anti-integrin therapies, and is under investigation for several cancers, including glioblastoma. Overall, studies in a variety of in vivo and in vitro models demonstrated that cilengitide:

- Blocks binding of α₅ integrins to the extracellular matrix
- Is anti-angiogenic
- Blocks endothelial cell proliferation
- Blocks adhesion, migration, and differentiation
- Induces apoptosis
- Displays additive activity in combination with a wide variety of classical and molecular targeted therapeutics

Phase 2 studies have demonstrated that cilengitide has only a modest effect in patients with recurrent glioblastoma. There are 2 large parallel phase 2 trials that have been completed in patients with newly diagnosed glioblastoma that were designed in response to the differing outcomes in patients based on MGMT promoter methylation status. In one of these phase 2 studies, CORE (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients with Newly Diagnosed Glioblastoma and Unmethylated Gene Promoter Status), patients were randomized to 3 arms: 1) standard of care radiation and temozolomide; 2) standard of care with cilengitide administered at the typical dose of 2,000 mg twice a week; or 3) standard of care plus the more dose-intensive cilengitide schedule of 5 times per week during radiation therapy. In the other phase 2 study, CECIL (Effect of Radiation Therapy Plus Temozolomide Combined With Cilengitide or Cetuximab on the 1-year Overall Survival of Patients With Newly Diagnosed MGMT-promoter Unmethylated Glioblastoma), cilengitide was compared with cetuximab, a monoclonal antibody directed against EGFR. This antibody is currently approved for the treatment of head and neck cancer and colorectal cancer. An eligibility criterion for both studies is unmethylated MGMT promoter status; that is, these tumors are considered to be resistant to the standard treatment of radiotherapy and temozolomide. This eligibility criterion was based on results from a European phase 1/2a trial, which demonstrated that when cilengitide was added to standard care, patients with MGMT promoter methylation had significantly longer median PFS and median OS than those without.

There is also a phase 3 study, CENTRIC (Cilengitide, Temozolomide, and Radiation Therapy in Treating Patients With Newly Diagnosed Glioblastoma and Methylated Gene Promoter Status), in which cilengitide 2,000 mg plus standard treatment was compared to standard treatment alone in patients with newly diagnosed glioblastoma who have methylated MGMT promoter status. These patients are expected to be more responsive to standard therapy than patients lacking promoter methylation. These cilengitide trials are all now closed and results are awaited.

In addition to integrin inhibitors, a variety of other targeted agents are being investigated in the treatment of glioblastoma (Table). The New Approaches to Brain Tumor Therapy (NABTT) Consortium accrued 365 patients with glioblastoma to 4 single-cohort studies with similar eligibility criteria. Patients received radiation therapy (RT) + temozolomide (TMZ) with talampanel (n = 72), poly-ICLC (n = 97), or cilengitide (n = 112), or RT + TMZ alone with monitoring of CD4 counts (n = 84). Overall survival of those aged 18 to 70 years with glioblastoma were compared to published data from the European Organisation for Research and Treatment of Cancer (EORTC). Results demonstrated that newly diagnosed glioblastoma treated recently with RT + TMZ and talampanel, poly-ICLC, or cilengitide had significantly longer survival than similar patients treated with only RT + TMZ accrued internationally from 2000 to 2002. These differences could result from the novel agents or changing patterns of care. The authors advised that until the reasons for these different survival rates are clarified, comparisons of outcomes from phase 2 studies with published RT + TMZ survival data should be interpreted with caution. The Radiation Therapy Oncology Group (RTOG) recently completed a phase 2 trial of conventional chemoradiation and adjuvant temozolomide plus cediranib vs. conventional chemoradiation and adjuvant temozolomide plus placebo in patients with newly diagnosed glioblastoma. A phase 2 and pharmacogenomics study of enzastaurin, a protein kinase C inhibitor, plus temozolomide during and following radiation therapy in patients with newly diagnosed glioblastoma multiforme and gliosarcoma showed that OS (median, 74 weeks) and PFS (median, 36 weeks) were comparable to those from a prior phase 2 study using erlotinib and were significantly better than those from 2 other previous studies that used thalidomide or cis-retinoic acid, all in combination with temozolomide.
plus RT. These studies suggest that the improvement in OS is more likely a reflection of an improvement in standard of care, recognition of pseudoprogression, and likely salvage therapy with bevacizumab.

In summary, there are a multitude of treatment modalities being investigated in the field of glioblastoma. Results of phase 3 clinical trials for various therapies are being anxiously awaited. There are also a plethora of investigational agents being studied, such as stem cell-targeted therapy, viral gene therapy, and antibody drug conjugates. Novel targeted agents such as histone deacetylase (HDAC) inhibitors, poly ADP ribose polymerase (PARP) inhibitors, VEGF pathway inhibitors, and mammalian target of rapamycin (mTOR) inhibitors, are being investigated as adjunctive treatments. There is hope that these targeted agents will improve survival outcomes in patients with this devastating disease.

References

Full references are available at www.healio.com/hematology-oncology/education-lab.
Perspectives on Glioblastoma Therapy

An interview with Marc C. Chamberlain, MD

Please comment on the safety of integrin inhibitors.

Marc C. Chamberlain, MD: They have a very low toxicity profile. One disadvantage to integrin inhibitors, however, is that they are intravenous therapies and require an injection twice a week, every week.

How would the FDA approval of an integrin inhibitor for the treatment of glioblastoma impact clinical practice?

Chamberlain: Integrin inhibitors did not demonstrate an improvement in the recurrent setting. The ongoing trials are examining their efficacy and safety in the upfront setting. If cilengitide were to be approved, it would be the first approved treatment for add-on therapy to standard of care. I think that, however, FDA approval will be challenging.

Are there any preliminary data on the safety of the vaccines being studied for the treatment of glioblastoma?

Chamberlain: I think that most of the preliminary data has come from ACT I, ACT II, and ACT III, which studied the EGFRvIII peptide vaccine. Results suggest that the safety profile of the vaccine is similar to cilengitide. Aside from injection-site reactions, there have been few to no issues with regards to toxicity. Furthermore, the vaccines are more convenient than cilengitide, as they are administered once a month. One critical issue with the vaccines is their use in patients with minimal disease burden. A patient with a large tumor should not be treated with a vaccine. However, the 2 large vaccine trials that are underway were lenient with those criteria in order to allow for a sufficient number of patients. I think that everyone in the field of cancer immunology would agree that the proper platform for immunotherapy is patients with image-verified complete resection. ACT IV and the clinical trial on DCVax are not really capturing those patients.

Of the therapies being studied for glioblastoma, which do you believe are the most promising?

Chamberlain: I believe the excitement in this field is focused on the immunological approach. This is a new treatment modality and a new mechanism of action that has not been well-explored, so there is a fair amount of anticipation and hope that this approach will be effective.

Are there any updates regarding recurrent disease?

Chamberlain: A device called Noxocure was approved by the FDA earlier this year to treat recurrent glioblastoma. This device utilizes an alternating electrical field, which penetrates the brain and inhibits the growth and proliferation of glioblastoma by interfering with tumor cell mitosis at anaphase.

At this year’s ASCO meeting there was much discussion about conducting trials in recurrent disease, because trials studying recurrent disease are almost always phase 2 single-arm studies. The few that progressed to phase 3 trials to date have all failed. This led to the question of whether clinical trials in the recurrent setting are being carried out in an appropriate manner.

There are 2 new studies in recurrent disease that are underway. In the phase 1/2 study RTOG 0929, a poly ADP ribose polymerase (PARP) inhibitor in combination with 2 different temozolomide schedules (days 1-21 of a 28-day cycle and days 1-5 of a 28-day cycle) is being studied in patients with recurrent disease. Also, the Adult Brain Tumor Consortium is conducting a phase 1 trial with a PARP inhibitor in newly diagnosed glioblastoma.
1. Which of the following is associated with increased survival in patients with glioblastoma?
   A. Methylated MGMT promoter compared with unmethylated
   B. Unmethylated MGMT promoter compared with methylated
   C. Treatment with dose-intensive temozolomide compared with standard of care
   D. Wild-type IDH-1 compared with mutated gene

2. Based on clinical trials to date, which of the following would be the most reasonable treatment in a patient with newly diagnosed glioblastoma?
   A. Concomitant radiotherapy and temozolomide for 6 weeks followed by temozolomide on days 1 through 21 of a 28-day cycle, with 6 to 12 cycles
   B. Concomitant radiotherapy and temozolomide for 6 weeks followed by temozolomide on days 1 through 5 of a 28-day cycle, with 6 to 12 cycles
   C. Concomitant radiotherapy and temozolomide for 6 weeks followed by temozolomide and nimotuzumab
   D. Concomitant radiotherapy and temozolomide for 6 weeks followed by temozolomide and cilengitide

3. Results of RTOG 0525 demonstrated that:
   A. Overall survival was similar in both groups.
   B. Radiation technique was a significant predictor of overall survival.
   C. Progression-free survival was significantly longer in the dose-intense group.
   D. Patients in the dose-intense group were more likely to have methylated MGMT.

4. According to safety analysis in the RTOG 0525 trial:
   A. The majority of patients who discontinued therapy did so because of treatment-related toxicity.
   B. There was a significant increase in grade 3, 4, and 5 toxicity in the dose-intense treatment arm.
   C. There was a significant increase in opportunistic infections in the dose-intense group.
   D. The incidence of fatigue was similar between the 2 groups.

5. The tissue molecular markers substudy performed in RTOG 0525:
   A. Are not amenable to widespread practice because they require frozen tissue.
   B. Included p53 mutation status.
   C. Correlated marker status to tumor histology.
   D. Produced 4 survival groups based on combinations of the markers.

6. The Net Clinical Benefits substudy:
   A. Found that the standard dose group experienced more symptoms from baseline to cycle 4.
   B. Did not find an association between neurocognitive and physical functioning quality of life at baseline and overall survival or progression-free survival.
   C. Found an association between neurocognitive and physical functioning quality of life changes from baseline to cycle 1 and overall survival and progression-free survival.
   D. Found a difference between treatment groups for symptoms, while both groups had similar cognition and neurological problems develop between baseline and cycle 1.

7. Which of the following statements is true?
   A. Nimotuzumab resulted in significant improvements in OS and PFS in the phase 3 study.
   B. Bevacizumab was shown to improve PFS but not OS in a phase 2 study that compared with the KPLA control group.
   C. Dendritic cell vaccines have been associated with toxicity issues.
   D. Poly-ICLC has been shown to have a survival advantage compared with non-temozolomide chemotherapy.

8. Which of the following treatments stimulates the immune system?
   A. Poly-ICLC
   B. Enzastaurin
   C. Integrins
   D. TGF-β

9. Cilengitide:
   A. Promotes angiogenesis.
   B. Blocks endothelial cell proliferation, adhesion, migration, and differentiation.
   C. Inhibits apoptosis.
   D. Was associated with a dramatic improvement in survival in patients with recurrent disease.

10. Rindopepimut is a peptide vaccine that:
    A. Had no effect on time to progression in phase 2 studies.
    B. Targets an EGFR variant that is typically expressed in both normal tissue and tumor tissue.
    C. Has shown high efficacy in preclinical models.
    D. Had no effect on overall survival in phase 2 studies.
Glioblastoma:
Current Perspectives, Clinical Challenges, and Trends in Treatment

POSTTEST

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