Management of malignant glioma: steady progress with multimodal approaches

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✓ Despite recent successes in the treatment of cancer with multidisciplinary multimodal treatment approaches, the duration of survival for patients with malignant glioma remains limited. Malignant gliomas represent a class of infiltrative, aggressive neoplasms that are generally resistant to combination therapies. The basic approach to treatment has involved a combination of surgery and radiotherapy. The use of chemotherapy has been met with skepticism because of its limited efficacy and the significant side effects demonstrated in clinical trials. Nevertheless, based on findings in randomized trials of new agents, it has been suggested that further evaluation of the role of chemotherapy is warranted. Temozolomide and Gliadel (carmustine wafers) are generally well tolerated due to their limited systemic toxicity. These agents appear particularly well suited for incorporation into multimodal treatment strategies. Proposed investigations and ongoing clinical trials will be conducted to assess the use of these agents in novel combination therapies. Future treatment strategies may include a wide variety of biological response modifiers, but will need to continue to address local control with surgery, radiation, and adjuvant chemotherapy.

KEY WORDS • glioma • temozolomide • Gliadel wafer • radiotherapy • chemotherapy • surgery

Tumors of the CNS

Epidemiological Features

Primary tumors of the CNS, from high-grade malignant gliomas and primitive neuroectodermal tumors to relatively benign meningiomas, neuromas, and adenomas of the pituitary gland, exhibit a range of behavior. In the most recent report from the Central Brain Tumor Registry of the US, researchers estimate that 7.3 new cases of primary malignant tumors of the CNS are diagnosed per 100,000 person-years. In 2005, there were 21,690 new cases of primary brain tumors, with 12,760 deaths recorded in the annual report of the Central Brain Tumor Registry of the US (2005–2006). Gliomas account for 42% of all primary CNS tumors and 77% of all malignant primary CNS tumors. Gliomas develop from diverse histological lineages, including but not restricted to oligodendroglioma, astrocytoma, and mixed oligoastrocytoma. Of these, low-grade and high-grade variants occur, but all have the potential to become highly malignant neoplasms that are recalcitrant to treatment, with GBM (World Health Organization Grade IV astrocytoma) being the most common and aggressive primary brain tumor in adults (Fig. 1).

Prognostic Factors

The prognosis for patients with CNS tumors is influenced by the histological features of the neoplasm, the age of the patient, and the neurological condition or functional status of the individual. In general, the effect of treatment on the overall prognosis has been surprisingly limited. Primary brain tumors, specifically gliomas, are difficult to treat and are generally considered incurable. Even the slower-growing tumors have the potential to recur and progress. Survival time is limited, and neurological morbidity from disease progression is high. Investigators participating in the GO Project reported on a large cohort (788 patients) with malignant glioma who underwent biopsy sampling or resection; the median duration of survival was 48 weeks for the overall population and only 40.9 weeks for patients with GBM.

Limitations of Current Treatments

Despite the efforts of research scientists and clinical investigators, progress in the treatment of malignant glioma has been limited until recent years. In the past, treatment for malignant gliomas frequently included resection or biopsy procedures followed by radiotherapy. The role of chemotherapy has been controversial; patients with malignant glioma typically have been treated at major brain tumor centers by medical and neurooncologists with special
training and interest in cancer of the CNS or as participants in clinical trials. Even with advances in neuroimaging, neurosurgical stereotactic navigation systems, and improved tumor control with targeted radiotherapy, recurrence is still nearly universal and survival duration is limited by the inevitable relapse and disease progression (Fig. 2). In the GO Project, half of the middle-aged patients (41–60 years old) with diagnoses of GBM and non-GBM lesions died within 53 and 85 weeks, respectively, post-treatment.

Historically, to achieve successful treatment of other more common cancers, clinicians had to overcome similar challenges to those presented by malignant gliomas. For example, the median survival time for patients with recurrent metastatic breast cancer has improved over the past few decades, from 15 months (1974–1979) to 58 months (1995–2000). It appears that this can be largely attributed to the advent of multimodal treatment strategies in which resection, radiotherapy, chemotherapy, and other bioactive agents are used. In the 1950s, surgery was the mainstay treatment for breast cancer with or without radiotherapy by the 1960s, adjuvant chemotherapy was introduced as single-agent therapy and then in multiagent combinations. Today, the addition of biological response modifiers, immune modulators, and targeted receptor blockers has resulted in better overall and disease-free survival rates for patients with breast cancer.

Established Therapies for Malignant Glioma

Advances in the treatment of malignant gliomas have lagged behind the strides made in treating extraneural tumors. Several additions to the armamentarium over the past several decades have led to improved outcomes; however, significant changes in the overall treatment paradigms have remained elusive. Patients who receive “supportive care” only, usually corticosteroid and anticonvulsant drugs, have a median survival duration of approximately 14 weeks or less (Fig. 2). As multimodal treatment strategies that include surgery, radiotherapy, and chemotherapy have been developed and used, the median survival time has improved, but not to the extent observed in other cancers, such as breast cancer.

Surgery and Radiotherapy. Historically, patients treated with surgery alone have a median survival duration of less than 6 months. The addition of postoperative radiotherapy extended the median survival time to approximately 9 months. In several studies, researchers have investigated various fractionation schedules, but none has demonstrated a significant benefit compared with stan-
standard dose schedules. Efforts to increase radiation doses to the local tumor region have included new techniques such as radiosurgery and brachytherapy, which have also met with limited success.

Systemic Chemotherapy. Historically, several factors have been proposed to explain the limited success of chemotherapy for malignant glioma, including the following: 1) intrinsic drug resistance; 2) tumor heterogeneity; and 3) failure to cross the BBB in sufficient amounts to reach and maintain therapeutic levels of cytotoxicity.

Various chemotherapy agents and combinations have been tested in randomized clinical trials over the past few decades. Stewart combined a total of 3004 patients from 12 studies performed between 1969 and 1991 to perform a metaanalysis to determine the overall efficacy of several agents, mostly nitrosoureas: carmustine, lomustine, nimustine, procarbazine, dacarbazine, and others. As a result of this analysis, found a significant prolongation of survival with the addition of chemotherapy (p < 0.0001), representing an increase in the 1-year survival rate from 40 to 46%, with an associated mean increase in survival of 2 months for those receiving chemotherapy compared with those treated with radiotherapy alone. Additionally, clinical trials testing chemotherapy for brain tumors have consistently confirmed that numerous factors, including patient age, performance status, and tumor grade, contribute to survival and likely influence the response to treatment. Recent pivotal work refining the classification of gliomas based on molecular genetic “signatures” has better defined the chemosensitive compared with chemoresistant subgroups of otherwise histologically identical tumors. These include 1p19q allelic analysis in oligodendroglioma and the DNA repair enzyme MGMT promoter methylation status in GBM.

Therapeutic Response to Nitrosoureas. Nitrosoureas such as BCNU have been widely studied in primary brain tumors because they have shown activity against gliomas in preclinical studies and have excellent BBB penetration. However, these agents have substantial hematopoietic, pulmonary, and renal toxicity, which limits their therapeutic utility. Adjuvant intravenously delivered nitrosoureas provided a slight benefit or no benefit when compared with radiotherapy alone. Fine, et al., performed a metaanalysis of 16 studies that were conducted over 15 years and involved more than 2350 patients with malignant glioma treated with radiotherapy with and without adjuvant chemotherapy. Nitrosoureas were used in most of these trials. These investigators estimated that the addition of chemotherapy following radiotherapy provided some benefit, prolonging survival from a median of 9.4 months to 12 months. Similar results were observed in a more recent metaanalysis that included 3004 patients, indicating a survival advantage of 2 months with the addition of chemotherapy to radiotherapy.

Combination Chemotherapy With Nitrosoureas. Efforts to reduce drug resistance and improve efficacy led to combination therapy with PCV. Initially, PCV was shown to have some activity against anaplastic oligodendroglioma, but in a recent Medical Research Council study of 674 patients with malignant glioma, investigators failed to demonstrate a survival advantage when PCV was added to radiotherapy compared with radiotherapy alone following resection. Despite the widespread assumption that PCV is well tolerated, significant myelosuppression and other adverse events often prevented completion of the full six-cycle course of recommended treatment.

Response to Platinum-Based Regimens. Several attempts to use platinum-based regimens (carboplatin and cisplatin) have failed to demonstrate an overall survival advantage over BCNU alone, despite an initial objective radiographically confirmed response. Specifically, the use of concurrent infused BCNU and cisplatin has not resulted in demonstrably improved survival over standard systemic BCNU in patients with GBM.
Despite the limited efficacy of chemotherapy in most patients with malignant glioma, we have inferred from some studies that the use of chemotherapy in multimodal regimens may be a contributing factor to long-term survival. Our review of clinical studies by Chamberlain and Kormanik leads us to suggest that the addition of chemotherapy to surgery and radiation improves long-term survival, particularly for patients with GBM, with a 5-year survival rate of 18% for patients receiving surgery, radiotherapy, and chemotherapy compared with 0% for those receiving surgery and radiotherapy alone. Furthermore, in an additional population-based study, it was suggested that the use of aggressive surgery and adjunct chemotherapy may improve the likelihood of long-term survival in selected patients with GBM. As recently as 2001, conventional management of malignant glioma in some centers still consisted of surgery and radiotherapy only. In 2005, researchers working on the GO Project reported that the use of chemotherapy in the management of malignant glioma was infrequent, despite the evidence that the addition of chemotherapy is associated with longer survival.

New Emphasis on Tumor Control With Local Treatment

In recent years, highly focused radiation and locally administered chemotherapy modalities have been developed to deliver aggressive antitumor treatment directly to the lesion site while minimizing exposure to adjacent areas of the brain and reducing systemic toxicity.

Radiosurgery and Brachytherapy. In general, the results of investigations in which the focal radiation dose is increased by numerous fractionation schedules or focal boost techniques, even to total doses of 120 Gy, have been disappointing. The ongoing failure of dose escalation to affect survival in this disease has been a sobering disappointment. The most popular methods of adding radiation doses are stereotactic radiosurgery and brachytherapy (with or without hyperthermia) with seed implants or the implantation of a novel brachytherapy device called the GliaSite Radiation Therapy System (Cytyc Corp., Marlborough, MA).

Radiosurgery. The initial enthusiasm for the use of stereotactically guided radiosurgery to provide a technique for increasing the focal radiation dose as an adjunct in glioma management appears to have lost momentum after publication of a large Phase III study conducted by the Radiation Therapy Oncology Group. In this study, patients with newly diagnosed malignant glioma were randomized to receive either fractionated radiation therapy plus BCNU or fractionated radiation therapy plus BCNU plus radiosurgery (either a linear accelerator–based system or the Gamma Knife was allowed). This study failed to demonstrate a survival advantage for the patients who received an additional radiosurgical boost as part of the initial management strategy.

Brachytherapy. Two large Phase III trials have been conducted in which standard radiotherapy alone was compared with standard radiotherapy plus low-activity iodine-125 seeds, with no significant survival advantage demonstrated by the addition of brachytherapy. Smaller Phase II studies yielded variable results. The addition of hyperthermia to brachytherapy demonstrated a statistically significant survival advantage in two small patient cohorts, but despite the favorable results, no large-scale, randomized study has been published to confirm these findings. The implantation of permanent iodine-125 seeds has also become popular and is favored by some radiation oncologists. Permanent, low-activity seeds appear to be favored in these trials because of the lower rate of radiation necrosis compared with that resulting from implantation of temporary, high-activity seeds. A novel approach to brachytherapy is the GliaSite Radiation Therapy System, a balloon catheter system implanted in the surgical cavity that includes a reservoir to hold an aqueous solution of organically bound iodine-125 (Iotrex [sodium 3-([125]I)-iodo-4-hydroxybenzenesulfonate]) to deliver low-dose radiation through a subcutaneous port. Although this approach has been shown to be feasible and safe in patients with recurrent malignant glioma, it has yet to achieve widespread use because of the lack of large-scale, randomized clinical data; the inconvenience to the patient, who needs to be isolated during treatment; and the necessity of a second surgery to remove the delivery system once treatment is completed.

The first efficacy study was recently published in which GliaSite brachytherapy was assessed in 24 patients with recurrent GBM. The median survival duration following GliaSite treatment was 9.1 months, and appeared comparable to historical data. Patients with a Karnofsky Performance Scale score of at least 70 survived longer than those with a score less than 70 (9.3 compared with 3.1 months; p < 0.003). GliaSite is a very attractive device for patients with small, superficial lesions that are considered resectable, but large, randomized trials will be needed to test any meaningful efficacy. We hope that the results will not prove as disappointing in analysis as have those in previous radiosurgery and brachytherapy trials.

Recent Advances

New FDA-Approved Treatments for Malignant Glioma

Although only incremental success has been observed for use of radiation therapy and chemotherapy in malignant glioma in the past 20 years, two agents introduced since 1996 have demonstrated clinical benefit in extending survival in patients with malignant glioma. Recently, the FDA approved these treatments for brain tumors; novel local therapeutic methods (Gliadel wafer) and systemic chemotherapy (TMZ) were included. These therapies have set new benchmarks for success in treating malignant gliomas. Despite the popularity of PCV and the preference of many clinicians for this form of multagent chemotherapy, the gold standard in measuring efficacy of any new adjuvant treatment has been radiotherapy alone or radiotherapy plus intravascularly delivered BCNU.

The Gliadel Wafer. Gliadel is a biodegradable polymer wafer impregnated with BCNU. The wafer is a 1.4 cm × 1 mm disc fashioned from polipropylene (20:80 poly [bis[p-carboxyphenoxy] propane/sebacic acid] containing 3.85% BCNU. At the time of resection, up to eight wafers are implanted into the surgical cavity (Fig. 3). Water in the intrstitial fluid causes the polymer slowly to degrade. The BCNU is thus released in a controlled
manner over several days to weeks and diffuses into the brain parenchyma at a high dose density. Concentrations as high as 1200 times more than those achieved by intravenous infusion have been observed, with minimal systemic exposure. Gliadel remains the only FDA-approved local chemotherapeutic agent indicated as a surgical adjunct for newly diagnosed malignant glioma and recurrent GBM. (See Gliadel prescribing information [Baltimore, MD: Guilford Pharmaceuticals Inc.; 2003]. Available at http://www.gliadel.com/pdf/PI_03_01_04.pdf. Accessed 8 September 2004.)

Used in this manner, Gliadel has been one of the few treatment modalities to demonstrate a statistical benefit in patients with malignant glioma, both in prolonging survival and in maintaining neurological function and performance status. Originally approved by the FDA in 1996 for use in recurrent GBM, Gliadel was approved in 2003 for initial treatment of all high-grade malignant glioma histological types at first diagnosis. Currently, a number of ongoing studies are being performed to investigate the safety and efficacy of combining local therapies, such as Gliadel, with other systemic agents, biological response modifiers, immunotherapy, and chemotherapy as part of multimodal, multiagent strategies.

Gliadel for Recurrent GBM. Table 1 summarizes key clinical trials in patients with recurrent brain tumors treated with Gliadel that led to its FDA approval. In recurrent malignant glioma, a Phase I/II dose-finding study in which BCNU wafer monotherapy was used in 21 patients resulted in 86% of them remaining alive for more than 1 year from initial diagnosis, and 38% lived more than 1 year from the time of implantation. Subsequently, in a large, double-blind, placebo-controlled, multicenter study conducted at the member institutions of the Polymere Treatment Group, 222 patients with recurrent malignant glioma were randomized to receive either Gliadel or placebo wafers at the time of repeated operation for recurrent or progressive disease. Numerous previous therapies had failed in the patients enrolled in this study, and they had undergone up to five previous craniotomies for resection. All patients had undergone previous radiation therapy with or without chemotherapy. In this heavily pretreated group, salvage therapy with Gliadel resulted in an 8-week net increase in median survival duration over that achieved with placebo for the intent-to-treat population (Fig. 4). Among the 145 patients with GBM, the addition of Gliadel significantly improved the 6-month survival rate, to 56%, compared with 36% for patients with GBM who received the placebo wafer (p = 0.02).

Gliadel for Newly Diagnosed High-Grade Malignant Glioma. A series of prospective studies were conducted in which BCNU polymeric chemotherapy was evaluated. Initially, a Phase I trial of 22 patients treated with Gliadel and postoperative radiotherapy indicated a median survival duration of 10.5 weeks and a 36% 1-year survival rate, with acceptable toxicity (Table 1). Following this, Valtonen, et al., described the results of a Phase III randomized placebo-controlled trial of Gliadel used in conjunction with resection and radiotherapy in newly diagnosed malignant glioma. The intent was to enroll 100 patients, but due to unavailability of the Gliadel for a period of time, the study was closed early to enrollment. The patients continued to be followed in blinded fashion for 2 years. There were 16 patients in each group, but only 11 with GBM were in the Gliadel group compared with 16 in the control group. The median survival duration for patients with GBM in the two groups was 13.3 months for the Gliadel group compared with 10 months for control, which despite the limited numbers of patients was statistically significant (p = 0.0008). At 3 years, four patients with GBM were still living, three of whom were in the Gliadel treatment group.

More recently, Westphal, et al., completed a larger randomized placebo-controlled Phase III trial of nearly identical design to the earlier trial of Valtonen, et al. Two hundred forty patients with newly diagnosed malignant glioma were randomized into two groups: in one the treatment consisted of surgery and placement of the Gliadel wafer, followed by postoperative radiotherapy, and in the other the treatment included surgery, placement of a placebo wafer, and postoperative radiotherapy.

In the intent-to-treat analysis, the Gliadel group had a statistically significant survival advantage (13.9 months compared with 11.6 months [p = 0.03]; see Table 1 and Fig. 5). Analysis of a variety of neurological performance measures indicated that the quality of life roughly paralleled survival duration. There was an imbalance in the number of patients with GBM between the two groups (101 compared with 106); however, evaluation with a Cox proportional hazards model indicated that the survival advantage was maintained in the GBM subgroup, with a risk reduction of 31% (95% CI 3–51%). In addition, more patients in the control group underwent a second operation, with a significant effect on overall survival. Censoring the groups for this second procedure yielded a significant effect on the analysis and indicated a median survival duration of 14.8 months compared with 11.4 months (p = 0.02).

A metaanalysis has also been reported, in which the two randomized studies were combined. Specifically, in the GBM group a survival benefit was noted (13.1 months for the Gliadel-treated groups compared with 10.9 months for placebo; p = 0.03), and in standard multivariate analysis...
This benefit was associated with a 29% reduction in risk of death (hazard ratio 0.71, 95% CI 0.54–0.95%; p = 0.02). In March 2003, the combination of the results of these studies led to FDA approval of Gliadel in the treatment of patients with newly diagnosed malignant glioma.

Temozolomide. Historically, because of the marginal benefit of systemic chemotherapy in treating malignant glioma, medical oncologists did not commonly encourage its application except in a clinical trial, unless they were part of a neurooncology team at a major brain tumor center. Recently, however, TMZ has gained well-deserved popularity because of its indisputable efficacy, ease of oral administration, and modest side-effect profile. This agent is being considered as part of multimodal regimens in structured clinical trials to better define its appropriate use for anaplastic astrocytoma, oligodendroglioma, lymphoma, and brain metastasis.

Temozolomide (3,4-dihydro-3-methyl-4-oxoimidazo[5,1-d]as-tetrazine-8-carboxamide), is an orally administered systemic alkylating agent that crosses the BBB. Its bioavailability is essentially 100%, with peak plasma concentrations occurring at 1 hour after dosing. This drug is spontaneously hydrolyzed at physiological pH to 3-methyl-(triazen-1-yl)imidazole-4-carboxamide, which is further hydrolyzed to methylhydrazine, the active alkylating species. The principal cytotoxic mechanism appears to be methylation of DNA. Although TMZ was originally tested and approved for a 5-day schedule every 28 days, extended-dose schedules continue to be studied. An extended dosing schedule is believed to deplete MGMT, an enzyme implicated in tumor resistance to alkylating agents. Depletion of MGMT is associated with longer median survival times in patients who are receiving alkylating agents, although this may be related to a subset of patients who demonstrate MGMT upregulation.

Activity of TMZ for Recurrent Anaplastic Astrocytoma at First Relapse. A Phase II trial of TMZ was conducted at L. S. Ashby and T. C. Ryken

### TABLE 1

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<tr>
<th>Authors &amp; Year</th>
<th>Study Type</th>
<th>Tumor</th>
<th>Treatment†</th>
<th>Median Increase RR (%)</th>
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<th>Authors &amp; Year</th>
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<td>12.1 mos — —</td>
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* DBPC = double-blind placebo-controlled; NS = not significant; rec = recurrent; retro = retrospective; RR = risk reduction; RT = radiotherapy; — = not applicable.
† All treatments with Gliadel include resection.
‡ For 39 patients with GBM.
§ Reported in Temodal product information (p = 0.33), and not in the study.

![Fig. 4. Graph showing Kaplan–Meier survival curve of patients with recurrent GBM treated with Gliadel wafer and radiation therapy after adjustment for prognostic factors. Reprinted from The Lancet, vol. 345, Brem H, Piantadosi S, Burger PC, et al: Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group, 1008–1012, copyright 1995, with permission from Elsevier.](unauthenticated|downloaded 06/17/22 02:29 AM UTC)
first relapse in 162 patients with malignant glioma, after treatment with radiotherapy and systemic nitrosourea (with or without procarbazine). A histological review confirmed a diagnosis of anaplastic astrocytoma or anaplastic oligoastrocytoma in 111 of these patients. The median overall survival duration was 13.6 months and the median progression-free survival was 5.4 months; the 12-month survival rate was 56%. The investigators concluded that TMZ demonstrated good single-agent activity (Table 1).

In another Phase II trial, TMZ was compared with a standard procarbazine regimen at first relapse in 225 patients with confirmed recurrent GBM. The median survival duration was 7.3 months for patients treated with TMZ compared with 5.7 months for those treated with procarbazine (p = not significant, Table 1). (See Temodal: Summary of product characteristics, 2005. Available at http://www.emea.eu.int/humandocs/PDFs/EPAR/Temodal/H-229-Pl-en.pdf. Accessed 12 January 2006.)

The 6-month survival rate and median progression-free survival were different: 60% compared with 44% (p = 0.019) and 12.4 weeks compared with 8.32 weeks (p = 0.0063) in the TMZ and procarbazine groups, respectively. It was also noted that health-related quality of life measures were maintained in patients who were free of tumor progression at 6 months. Based on these and other studies, TMZ was approved in the US in 1999 for patients with recurrent anaplastic astrocytoma who have experienced disease progression after radiotherapy and initial treatment with a drug regimen containing a nitrosourea and procarbazine. (See Temodar product information, available at http://www.spfiles.com/pitemodar.pdf. Accessed 11 May 2005).

Use of TMZ in Newly Diagnosed GBM. The agent TMZ has also shown efficacy in newly diagnosed malignant glioma. In an open-label, Phase II study, 64 patients with newly diagnosed GBM were treated with concurrent TMZ and radiotherapy, followed by adjuvant TMZ administered for 5 days every 28 days for six cycles. The median survival period for these patients was 16 months, with 1- and 2-year survival rates of 58 and 31%, respectively (Table 1). Based on the favorable findings in this preliminary Phase II study, the European Organisation for Research and Treatment of Cancer Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group initiated a randomized, multicenter, Phase III trial to evaluate the benefit of adding TMZ to radiotherapy compared with radiotherapy alone for newly diagnosed GBM. In this study, 573 patients were randomized to two treatment groups: 1) fractionated involved-field radiotherapy (2 Gy once daily, 5 days per
week for 6 weeks; 60 Gy total), or 2) the same radiotherapy schedule plus concurrent daily TMZ (75 mg/m²/day) followed by up to six cycles of monthly adjuvant TMZ (150–200 mg/m²/day for 5 days). The median survival duration was 14.6 months (95% CI 13.2–16.8 months) in patients who received radiotherapy plus TMZ, compared with 12.1 months (95% CI 11.2–13 months) in those who received radiotherapy alone, resulting in an increase in median survival duration of 2.5 months (Table 1, Fig. 6). The 2-year survival rate was 26.5% (95% CI 21.2–31.7%) for TMZ compared with 10.4% for radiotherapy alone (95% CI 6.8–14.1%). Grade 3 or 4 hematological toxicity occurred in 16% of patients in the TMZ group during concurrent or adjuvant treatment.

Recently, a retrospective analysis of the European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada trial data was performed to assess the impact of resection on survival. Prior to treatment with radiotherapy with or without TMZ, 39% of patients underwent complete resection of tumor tissue, 44% attained a partial resection, and 16% underwent biopsy sampling only. The survival benefit with TMZ was evident in all cohorts but was more pronounced in patients who underwent complete resection. The median survival duration in patients in whom a complete resection was achieved was 18.3 months (95% CI 15.7–22.5 months) in the radiotherapy plus TMZ group and 14.2 months (95% CI 12.7–16.2 months) in the group undergoing radiotherapy alone. The corresponding results in the groups treated with radiotherapy plus TMZ and radiotherapy alone were 13.5 months (95% CI 11.9–16.3 months) and 11.7 months (95% CI 9.7–13.1 months), respectively, for patients in whom partial resection was performed and 9.4 months (95% CI 7.5–13.2 months) and 7.9 months (95% CI 5.4–10.6 months), respectively, for patients who underwent biopsy sampling only.

The results reported in the Phase III trial are favorable when compared with historical data on systemic chemotherapy for this disease. It should be noted that slides were not available for confirmation of histological diagnosis in 15% of the cases and that 7% of patients had histologically confirmed non-GBM or unconfirmed histological features, pointing out the importance of tissue availability for pathological review of CNS disease. The addition of TMZ resulted in a clinically meaningful and statistically significant survival benefit for patients with newly diagnosed malignant glioma, and led to FDA approval in March 2005 for use as initial therapy in patients with GBM. Toxicity is mainly hematological, with only a minority of patients requiring any kind of replacement transfusion or bone marrow support. Gastrointestinal side effects are also mild to moderate. To prevent the possibility of developing the lymphocytopenia and opportunistic infection associated with TMZ in earlier trials, the patients randomized to receive this agent were prophylactically given inhaled pentamidine or orally administered trimethoprim–sulfamethoxazole against Pneumocystis carinii pneumonia.
Advancements in Treatment of Brain Tumors: Multimodal Therapies

The consensus of the data supports the contention that no chemotherapy agent alone can effectively treat high-grade malignant gliomas, nor can surgery or radiation therapy alone. Neither Gliadel nor TMZ represent the “home run” we hope for in the treatment of this deadly disease. Gliadel resulted in a median increase in survival of 2 and 2.3 months for recurrent and newly diagnosed GBM, respectively. When given concurrently with radiation, TMZ resulted in an increased median survival time of only 2.5 months compared with radiation therapy alone. In fact, the mean increase in survival time is only slightly better than that achieved in any of the 12 studies summarized in Stewart’s metaanalysis of prior investigations. The future use of these agents will likely be as integrated treatment with target-specific molecules as well as with other antineoplastic drugs. Use of TMZ in combination with other antineoplastic agents, including cisplatin, irinotecan, thalidomide, retinoic acid, tamoxifen, and O6-benzylguanine is being tested. Likewise, in several Phase I/II studies, Gliadel has been combined with PCV, TMZ, irinotecan, or carboplatin.

The combination of TMZ and Gliadel is especially interesting because of the ability of TMZ to deplete the DNA repair enzyme responsible for BCNU resistance. Preclinical studies support the suggestion that MGMT is part of the resistance mechanism and that synergy or additive effects of the combination of BCNU and TMZ may be due in part to the depletion of this repair enzyme. A combination study of TMZ and intravenous BCNU for treatment of advanced solid neoplasms in 63 patients resulted in significant hematological toxicity and limited the TMZ dose to 110 mg/m2/day. Similar results have been reported in patients with glioma. Raizer, et al., found that the maximum tolerated dose for a 28-day cycle of TMZ was 80 mg/m2/day when used in combination with intravenous BCNU, and they concluded that long-term combined systemic therapies may not be feasible because of exaggerated myelosuppression.

On the other hand, a Phase I dose-ranging study demonstrated the safety of the combination of Gliadel and TMZ in 10 patients with recurrent supratentorial high-grade glioma. Up to eight wafers were positioned in the surgical cavity after resection. The TMZ (100, 150, or 200 mg/m2/day) was given orally for 5 days beginning 2 weeks postsurgery. Treatment was well tolerated with no new or unexpected toxicities, even at the highest standard dose of 200 mg/m2/day, demonstrating that TMZ can be administered safely after placement of Gliadel wafers. Two patients were alive without disease progression after 12 months of the combined treatment.

Preliminary data from a Phase II multicenter trial were obtained in 16 patients with surgically accessible, high-grade, newly diagnosed malignant glioma. Following resection and Gliadel wafer placement, patients underwent radiation therapy plus concurrent TMZ (75 mg/m2, 7 days per week) followed by a monthly standard schedule of adjuvant TMZ (200 mg/m2 daily for 5 days every 28 days, < 18 cycles). After a median follow-up period of 7 months, the median and progression-free survival times had not been reached, and the 1-year survival rate was 63%.

Gliadel and TMZ are also being investigated as part of other combination chemotherapy regimens or multimodal strategies (Table 2). Gliadel is being evaluated in combination with irinotecan, carboplatin, and other agents including O6-benzylguanine (an inhibitor of MGMT). In addition, studies have been conducted to investigate the use of concurrent Gliadel and brachytherapy with the GliSite system or 125I seeds, and the combination of Gliadel and radiosurgery. Other studies with Gliadel include the evaluation of higher BCNU doses in the polymers, which may penetrate surrounding brain tissue for greater distances. Gliadel is also being tested in the surgical management of brain metastases, and preliminary analysis has shown exceptional local tumor control rates.

Conclusions

An improved understanding of the pathogenesis of malignant glioma and the rationale for development of therapeutic agents will depend on advances in molecular genetics and the development of therapies targeting critical steps in signal pathways that have yet to be fully elaborated. In the meantime, multidisciplinary, multimodal anticancer treatments will continue to include surgery, radiotherapy, and combination chemotherapy with the addition of immunotherapy and biological response modifiers. Progress continues with novel approaches, including con-

TABLE 2

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Authors &amp; Year</th>
<th>No. of Patients &amp; Histological Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gliadel</td>
<td>Limentani, et al., 2005</td>
<td>16 w/ initial MG</td>
</tr>
<tr>
<td>TMZ</td>
<td>Gururangan, et al., 2001</td>
<td>10 w/ rec MG</td>
</tr>
<tr>
<td>PCV</td>
<td>LaRocca, et al., 2005</td>
<td>16 w/ initial MG</td>
</tr>
<tr>
<td>irinotecan</td>
<td>Sampath, et al., 2005</td>
<td>9 w/ initial MG</td>
</tr>
<tr>
<td>O6-benzylguanine</td>
<td>Rosenblum, et al., 2002</td>
<td>10 w/ rec GBM</td>
</tr>
<tr>
<td>iodine-125 seeds</td>
<td>Darakchiev, et al., 2004</td>
<td>31 w/ rec MG</td>
</tr>
<tr>
<td>TMZ</td>
<td>Foltz, et al., 2005</td>
<td>10 w/ rec GBM</td>
</tr>
<tr>
<td>Gliadel</td>
<td>Zamorano, et al., 2005</td>
<td>6 w/ initial or rec GBM</td>
</tr>
<tr>
<td>TMZ</td>
<td>Tozer, et al., 2003</td>
<td>16 w/ rec MG</td>
</tr>
<tr>
<td>GliaSite RTS radiosurgery</td>
<td>Sampath, et al., 2005</td>
<td>24 w/ rec GBM</td>
</tr>
<tr>
<td>TMZ</td>
<td>Smith, et al., 2004</td>
<td>19 w/ initial GBM</td>
</tr>
<tr>
<td>TMZ</td>
<td>Balà, et al., 2004</td>
<td>40 w/ initial GBM</td>
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<tr>
<td>TMZ</td>
<td>Silvani, et al., 2004</td>
<td>33 w/ rec MG</td>
</tr>
<tr>
<td>TMZ</td>
<td>Marzolini, et al., 1998</td>
<td>2 w/ rec MG</td>
</tr>
<tr>
<td>TMZ</td>
<td>Raizer, et al., 2004</td>
<td>24 w/ initial MG</td>
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<td>TMZ</td>
<td>Chang, et al., 2004</td>
<td>67 w/ initial GBM</td>
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<td>TMZ</td>
<td>Butowski, et al., 2005</td>
<td>61 w/ initial GBM</td>
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<td>TMZ</td>
<td>Spence, et al., 2004</td>
<td>16 w/ rec MG</td>
</tr>
<tr>
<td>TMZ</td>
<td>Quinn, et al., 2005</td>
<td>38 w/ rec MG</td>
</tr>
</tbody>
</table>

* MG = malignant glioma; RTS = radiation therapy system.
vection-enhanced delivery, gene therapy, dendritic vaccination, biological response modifiers, and novel forms of delivery.

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