Current Standard Treatment Options for Malignant Glioma

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Introduction

The Central Brain Tumor Registry estimates that there will be more than 24,000 new cases of primary malignant brain and central nervous system (CNS) tumors diagnosed in the United States in the year 2016. Eighty percent or more than 19,000 of these cases will be malignant gliomas consisting of World Health Organization (WHO) grade 3 anaplastic tumors and grade 4 glioblastoma. WHO grade 3 tumors can be further broken down into threes anaplastic subtypes: astrocytoma, oligodendroglioma, and oligoastrocytoma based upon morphologic and molecular features.

Glioblastoma is the most common (46%) and aggressive primary malignant brain tumor (Fig. 8.1a). WHO grade 4 tumors are distinguished from grade 3 tumors by the presence of pseudopalisading necrosis and vascular proliferation which are morphologic hallmarks of their aggressive nature. Except in rare circumstances, glioblastoma is a fatal diagnosis with current median overall survival of 15–23 months and a five-year survival of less than 5% [1].

Anaplastic gliomas (Fig. 8.1b) can be defined based upon morphologic features of increased hypercellularity, nuclear atypia with alteration of the nuclear–cytoplasmic ratio, and increased mitotic activity. Although early studies often did not distinguish among the various subtypes (or even WHO grade 3 from grade 4 tumors), we now know that the oligodendroglioma feature is often associated with 1p/19q co-deletion and a favorable prognosis. The current median life expectancy after diagnosis of a WHO grade 3 tumor is 2–3 years [2] for the general patient population; however, this can be further broken down when taking into account IDH1 mutation status and 1p/19 co-deletion [3].

Chemotherapy

Nitrosoureas

Nitrosoureas such as carmustine (BCNU) and lomustine (CCNU) are highly lipophilic compounds that exhibit excellent blood–brain barrier penetration with lomustine reaching brain concentrations nearly equal to serum levels. Nitrosoureas are spontaneously broken down into two active metabolites; chloroethyldiazohydroxide and an isocyanate group. The chloroethyldiazohydroxide moiety mediates DNA–DNA and DNA–protein cross-linking and the isocyanate group carbamoylates amino acids which leads to disruption of RNA synthesis and DNA repair.

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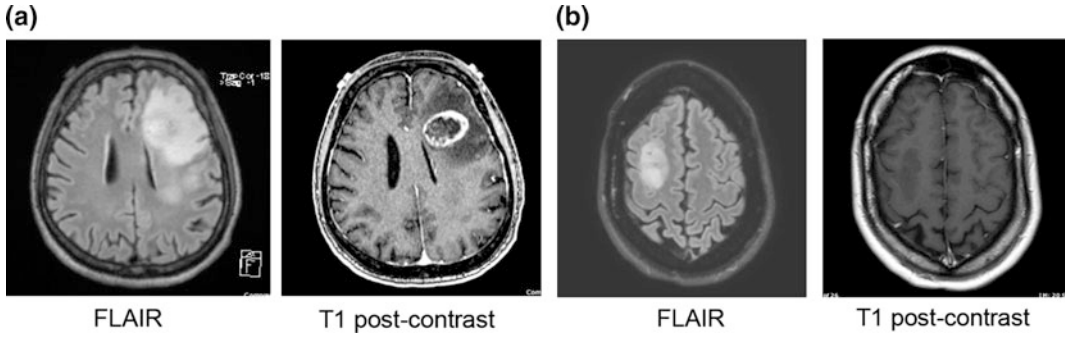

Fig. 8.1 **a** Magnetic resonance imaging of brain—glioblastoma magnetic resonance imaging reveals the aggressive nature of glioblastoma with the typical ring enhancement, central necrosis, and significant mass effect. **b** Magnetic resonance imaging of brain—anaplastic astrocytoma. Magnetic resonance imaging demonstrates the radiographic features of a WHO grade III anaplastic astrocytoma with bulky FLAIR signal suggestive of mass and absence of contrast enhancement

The use of these agents is dose-limited by cumulative myelosuppression and potential pulmonary toxicity.

Nitrosoureas—Newly Diagnosed Anaplastic Gliomas

Historically, nitrosoureas have been the most common chemotherapy class used in the management of malignant gliomas with widespread use since the 1970s. The approval of temozolomide in March 2005, with its improved adverse effect profile and efficacy, largely relegated these agents to the treatment of recurrent disease with several notable exceptions. In the RTOG 9402 clinical trial, lomustine combined with vincristine and procarbazine as part of the "PCV protocol" was evaluated for newly diagnosed malignant gliomas [4]. In this study, 291 patients with either anaplastic oligodendroglioma or anaplastic oligoastrocytoma were randomized to receive radiation therapy alone or up to 4 cycles of PCV chemotherapy followed by radiation therapy. In the end, there was no difference in median survival between the PCV-radiation group versus the radiation therapy-alone group (4.6 vs. 4.7 years; hazard ratio [HR] = 0.79; 95% CI, 0.60–1.04); however, subgroup analysis demonstrated that patients with 1p/19q co-deletions had a significant survival advantage when treated with PCV radiation compared to patients treated with radiation therapy alone (14.7 vs. 7.3 years; HR = 0.59; 95% CI, 0.37–0.95; $p = 0.03$). These findings suggested that 1p/19q co-deletion was predictive for chemotherapy response.

A role for the use of PCV chemotherapy for patients with 1p/19 co-deleted tumors was further defined by the findings of EORTC 26951 clinical trial which randomized 368 patients with anaplastic oligodendroglioma or anaplastic oligoastrocytoma to receive either radiation therapy or radiation followed by up to six cycles of PCV [5]. Unlike the RTOG trial, survival in the radiation group combined with chemotherapy was prolonged versus the radiation therapy-alone group (42.3 vs. 30.6 months, hazard ratio [HR], 0.75; 95% CI, 0.60–0.95); however, in the 80 patients identified with 1p/19q co-deletion survival was further augmented by addition of PCV following radiation (OS not reached in the RT/PCV group versus 112 months; HR, 0.56; 95% CI, 0.31–1.03). These findings support the use of chemotherapy for malignant tumors with 1p/19q co-deletion, i.e., oligodendrogliomas and mixed gliomas.

Several questions arose out of these findings including whether temozolomide could be substituted for the PCV regimen and whether it is important to start with radiation followed by chemotherapy or chemotherapy followed by radiation. An attempt to address both these questions was undertaken with the NOA-04

clinical trial [6]. In this phase III clinical trial, patients with newly diagnosed anaplastic glioma were randomly assigned to receive either 60 Gy fractionated radiation, 4 cycles of PCV, or 8 cycles of temozolomide. At the time of disease progression or with the development of unacceptable toxicity, patients were then allowed to cross-over to receive either radiation (PCV and temozolomide arms) or PCV or temozolomide (radiation arm, randomized 1:1). Initial analysis revealed there were no differences between progression-free survival between the radiation versus chemotherapy group (30.6 months vs. 31.9 months, HR 1.0; $p = 0.87$) or median overall survival (72 months vs. 82 months, HR 1.2). This was further confirmed with long-term analysis after following patients for 11.8 years which showed there were no differences among the treatment groups [7]. Several conclusions arose out of this study. It appeared that PCV and temozolomide had equivalent efficacy at least for all gliomas and that there was no difference in survival whether patients were treated with radiation or chemotherapy upfront or at recurrence; however, the mature data from this trial have yet to be published in a peer-reviewed journal. Molecular analysis also revealed that isocitrate dehydrogenase 1 mutations were stronger positive prognostic factors than either MGMT methylation status or 1p/19 co-deletion.

There are ongoing studies including the Alliance trial—CODEL clinical trial which is currently recruiting patients with 1p/19q co-deleted anaplastic gliomas (astrocytoma, oligoastrocytoma, and oligodendroglioma) and WHO grade II low-grade gliomas. This study is evaluating temozolomide and PCV chemotherapy head to head following fractionated radiation therapy. Another trial, the EORTC 26053/RTOG 0834 CATNON phase III clinical trial is an ongoing study evaluating the timing of temozolomide and whether adding temozolomide to fractionated radiation is beneficial compared to radiation treatment alone for patients with 1p/19q intact anaplastic gliomas. Given the nature of clinical trials and the involvement of both low-grade and anaplastic tumors, it will likely be many years before we have definitive data regarding this important question; however, a general trend at least in the USA is to treat patients with oligodendrogliomas with PCV and other tumors with temozolomide.

Nitrosoureas—Recurrent Glioblastoma

The phase II "BELOB" clinical trial investigated the role of lomustine alone and combined with bevacizumab versus monotherapy bevacizumab for recurrent glioblastoma. This study enrolled 153 patients with recurrent glioblastoma who were randomized to receive either lomustine 110 mg/m^2 every 6 weeks, lomustine at either 90 or 110 mg/m^2 along with bevacizumab 10 mg/kg given every 2 weeks, or bevacizumab alone. The investigators found that the nine-month overall survival was 43% in the lomustine arm, 38% in the bevacizumab arm, and 63% in the bevacizumab and lomustine (combined 90 and 110 mg/m^2) arm and progression-free survival at 6 months was 13% for lomustine, 16% for bevacizumab, and 42% for combined bevacizumab and lomustine. Although these results appear to be an improvement over the results of bevacizumab and irinotecan studied in the BRAIN trial [8], a more definitive answer awaits the conclusions of the EORTC 26101 phase III clinical trial which has recently completed enrollment of patients with progressive glioblastoma to either lomustine 90 mg/m^2 every six weeks along with bevacizumab 10 mg/kg every two weeks versus monotherapy lomustine 110 mg/m^2 every six weeks.

The first clinical trial to prospectively evaluate nitrosoureas and temozolomide head to head for recurrent glioblastoma (and a small subset of anaplastic gliomas—26% of enrollees) was undertaken by Brada et al. [9]. In this study, 447 chemotherapy-naïve patients at first relapse following radiotherapy were randomized to receive either 6 cycles of PCV every six weeks or temozolomide at 150–200 mg/m^2/day on a 5 of 28-day schedule or 100 mg/m^2/day on a 21 of 28-day schedule. After a median follow-up time of 10.4 months for the PCV and 14 months for the temozolomide arm, there was no survival benefit seen when comparing PCV to the combined arms of temozolomide (6.7 months for

PCV and 7.2 months for combined temozolomide, HR 0.91; 95% CI 0.74–1.11, $p = 0.36$); however, the 5 of 28-day schedule of temozolomide did modestly improve survival compared to PCV (5 months for temozolomide and 3.6 months for PCV; HR 0.8; 95% CI, 0.63–1.03, $p = 0.038$). The conclusion of this trial was that PCV and temozolomide on a 5 of 28-day schedule were similar in efficacy but given an observed improvement in quality of life and ease of administration, temozolomide should be favored over PCV.

Temozolomide

Temozolomide is an oral alkylating chemotherapy agent whose drug development arose out of the clinical trial failure of dacarbazine and mitozolomide for patients with melanoma. At physiologic pH, temozolomide undergoes base catalyzation to monomethyl-triazeno-imidazole-carboxamide (MTIC) which spontaneously converts to the bio-reactive methyldiazonium cation. Methyldiazonium goes on to alkylate the N^7 and O^6 positions of guanine and N^3 position of O^6 alkylation of guanine is thought to mediate the predominant anti-tumor effect. Although early studies demonstrated a variety of adverse effects including fatigue, nausea/vomiting, and myelosuppression, these have proven to be relatively mild in clinical practice and predictable compared to previously used cytotoxic agents.

The first clinical trial evaluating temozolomide solely for malignant glioma was conducted by O'Reilly et al. [10] who enrolled 28 patients with 18 of the patients having a high-grade glioma. Of the 10 evaluable patients who received adjuvant temozolomide, 5 patients (4 had WHO grade IV tumors) experienced significant clinical and radiographic improvement. These findings led Roger Stupp and colleagues to design a phase II study and ultimately the seminal EORTC-NCIC phase III study which established temozolomide along with fractionated radiation followed by adjuvant temozolomide administered at 150–200 mg/m^2/day on a 5 of 28-day schedule as the standard of care for patients with newly diagnosed glioblastoma. This combination led to median survival ranges of 15–23 months or a 3- to 11-month median survival improvement beyond surgery followed by radiation therapy alone [11, 12].

An additional important finding that arose from the EORTC-NCIC trial was that patients with methyl-guanine-methyltransferase (MGMT) methylation were more responsive to temozolomide and had prolonged survival compared to patients with hypomethylated MGMT [13]. This led to the hypothesis that temozolomide given over a prolonged period could possibly lead to MGMT depletion and improved chemoresponsiveness. This theory was tested in a randomized phase II study which enrolled 85 patients with newly diagnosed glioblastoma treated with six weeks of concurrent radiation and temozolomide to receive adjuvant treatment with either dose-dense temozolomide (150 mg/m^2/day—7 days on, 7 days off) or metronomic (daily) temozolomide (50 mg/m^2/day) [14]. One-year survival for patients treated with the dose-dense regimen was 80% which was superior to metronomic dosing (69% survival at one year) and also an improvement from the 61% one-year survival observed with the EORTC-NCIC clinical trial [11]. This was further studied in the randomized phase III RTOG 0525 clinical trial which compared adjuvant temozolomide given on a 5 of 28-day schedule at 150–200 mg/m^2/day versus temozolomide at 75 mg/m^2/day on a 21 of 28-day schedule [15]. Both dosing schedules were given up to 12 cycles. No survival benefit was seen for dose-dense temozolomide (median overall survival 14.9 months, 95%, CI 13.7–16.5 months) versus standard dosing (16.6 months, 95% CI, 14.9–31.5 months, HR, 1.03, $p = 0.63$). On the basis of these studies and others [9], there is currently no role for dose-dense temozolomide for newly diagnosed glioblastoma.

Gliadel Wafers

Gliadel wafers are biodegradable wafers consisting of a poly (carboxyphenoxy-propane sebacic acid) matrix embedded with the

nitrosourea, carmustine (BCNU). The wafers were developed by Henry Brem and colleagues in an attempt to avoid the hematologic and pulmonary toxicity associated with the systemic administration of BCNU [16].

In 1993, Tamargo et al. were the first to demonstrate that the interstitial release of BCNU through BCNU-embedded polymer wafers was superior to systemic administration in a gliosarcoma animal model [17]. This ultimately led to a series of clinical trials for patients with malignant gliomas. Gliadel was approved by the Federal Drug Administration (FDA) in 1996 for the treatment of recurrent glioma on the basis of the findings of a phase III clinical trial. In this randomized, placebo-controlled trial, 222 patients with recurrent malignant glioma were randomized to receive either surgically implanted wafers embedded with 3.85% BCNU or placebo. The median overall survival for patients on the experimental arm was 31 weeks versus 23 weeks for patients receiving placebo wafers (HR = 0.67, $p = 0.06$). Subanalysis of glioblastoma patients demonstrated a survival advantage of 50 % at six months (44% vs. 64%, $p = 0.02$), and there were no significant adverse events observed [18].

A large, international, randomized phase III clinical trial [19] for patients with newly diagnosed malignant glioma was initiated after the encouraging results of a small randomized, placebo-controlled trial [20]. In this trial, 240 patients with newly diagnosed glioma were randomized to receive either BCNU wafer or placebo at the time of the initial surgical resection followed by fractionated radiation therapy. At the time of early follow-up (12–30 months), a survival benefit was observed for patients treated with BCNU wafers (13.9 vs. 11.6 months, $p = 0.03$). These findings were confirmed in a long-term (59 months) follow-up report [21]. A meta-analysis of these two trials by Meldorf et al. [22] further demonstrated a reduction in the risk of death of 29% with the implantation of BCNU wafers. On the basis of these findings, FDA approved Gliadel for patients with newly diagnosed glioma in 2003.

Although the development of Gliadel represented a significant advance for the treatment of newly diagnosed and recurrent glioma, their widespread use and acceptance has subsequently been limited due to a high rate of postoperative infections, problems with wound healing, chemical meningitis, cerebral edema, obstructive hydrocephalus, cyst formation, and pseudoprogression [23, 24].

Bevacizumab

Almost 50 years ago, Judah Folkman and colleagues hypothesized that targeting the tumor vasculature of solid tumors would represent an effective treatment strategy [25]. Ultimately, it was discovered that the family of soluble ligand vascular endothelial growth factor (VEGF) mediates tumor neovascularization in a wide range of tumors. VEGF was subsequently shown to be an important mediator of angiogenesis in malignant gliomas with 30-fold higher concentrations in glioblastoma when compared to low-grade gliomas [26]. Bevacizumab is a humanized monoclonal antibody that binds vascular endothelial growth factor with high affinity ($K_d \sim 0.5$ nM) and has been approved for a variety of tumors including relapsed glioblastoma [27]. Despite initial concerns about intra-cranial hemorrhage and stroke, bevacizumab has been shown to be well-tolerated agent and exhibits an extended half-life of approximately 21 days.

Bevacizumab—Recurrent Glioblastoma

The first clinical trial evaluating bevacizumab for malignant glioma was undertaken in 2004 with 21 patients (11 glioblastoma and 10 anaplastic astrocytoma) who were treated with bevacizumab 5 mg/kg and irinotecan 125 mg/m^2 every two weeks [28]. This was a seminal study as it demonstrated not only the safety of bevacizumab but also a response rate of 43% which was a significant improvement from historic controls. This led to several pivotal phase II studies in which bevacizumab was used as monotherapy or in combination with irinotecan for patients with recurrent glioblastoma [29–32].

These studies demonstrated dramatically improved imaging response rates of 28–35% with bevacizumab and progression-free survival at 6 months of 29–43%. On the basis of these phase II clinical trials, on May 5, 2009, the FDA approved bevacizumab monotherapy in the United States for recurrent glioblastoma.

Bevacizumab—Newly Diagnosed Glioblastoma

Two phase III clinical trials have been undertaken to address the role of bevacizumab in the upfront setting for newly diagnosed glioblastoma. The "Avaglio" or Avastin in glioblastoma trial was a double-blind, placebo-controlled trial that randomized 921 patients with newly diagnosed glioblastoma to receive the standard of care consisting of fractionated radiation and daily temozolomide at 75 mg/m^2/day followed by six cycles adjuvant temozolomide 150–200 mg/m^2/day on a 5 of 28-day schedule along with either q2weekly bevacizumab 10 mg/kg or placebo [33]. In the end, there was no improvement in overall survival between the groups (median overall survival of 16.8 months for bevacizumab-treated patients and 16.7 months for placebo control); however, there was an improvement in progression-free survival with the addition of bevacizumab (10.6 vs. 6.2 months, HR, 0.64, $p < 0.001$). In the RTOG 0825 clinical trial, Gilbert and colleagues randomized 637 patients with newly diagnosed glioblastoma to receive the standard of care consisting of concurrent fractionated radiation and temozolomide followed by up to 12 cycles of adjuvant temozolomide with either bevacizumab 10 m/kg or placebo administered two weeks [34]. Similar to the Avaglio trial, there was no improvement in the median overall survival with the addition of bevacizumab (15.7 months vs. 16.1 months for placebo arm), but there was a modest increase in progression-free survival (10.7 months vs. 7.3 months for placebo arm). Importantly, it is unknown what effect the high level of cross-over associated with this trial had on survival. As such, at this time there is no role for the regular use of bevacizumab upfront; however, it may be beneficial in defined subgroups (patients with large volume residual disease; molecularly identifiable subgroups).

NovoTTF

In 2004, Kirson and colleagues reported that the application of very low-intensity, intermediate-frequency (100–300 kHz), alternating electrical fields ("tumor treating fields or TTFields") could disrupt the normal formation of the mitotic spindle and cause growth inhibitory effects in both cell culture lines and animal models [35]. They went on to show that this occurred in a non-thermal manner and exposure to the alternating electrical field had no deleterious effect on non-dividing cells. The mechanism of action was thought to be related to the disruption of the normal polymerization–depolymerization process that is required for cell mitosis.

These findings led to the testing of alternating electrical fields in the Fischer rat glioma model where it was observed that increasing the number of TTField directions led to significant tumor growth inhibition. This inspired the development of a single-arm pilot study with 10 patients with relapsed glioblastoma. Progression-free survival at 6 months was 50% (23–77%; 85% confidence interval) and the median overall survival was 62 weeks (20–124 weeks) with two patients alive more than two years from the start of TTField [36]. There were no serious adverse events, and the only significant toxicity was mild to moderate dermatitis at the site of electrode contact. Further studies demonstrated that the TTFields were safe and additive when administered in conjunction with chemotherapy in cell lines and animal model. As part of this publication, additional pilot studies were conducted with 10 patients with relapsed glioblastoma (failed first line) and 10 patients with newly diagnosed glioblastoma who received the TTFields along with adjuvant temozolomide [37].

NovoTTF—Newly Diagnosed Glioblastoma

A randomized, non-blinded clinical trial was initiated in July 2009 evaluating the application of TTFields in patients with newly diagnosed glioblastoma [38]. In total, 695 patients with histologically confirmed glioblastoma were randomized 2:1 to receive either adjuvant temozolomide 150–200 mg/m^2/day on a 5 of 28-day schedule along with NovoTTF delivered continuously >18 h per day or temozolomide alone. This trial was terminated prematurely after an interim analysis revealed a survival benefit. The interim analysis included 210 patients randomized to receive TTFields and temozolomide and 105 patients randomized to temozolomide alone. The median progression-free survival was 7.5 months (95% CI, 5.9–8.2 months) versus 4.0 months (95% CI, 3.3–5.2 months) in the temozolomide arm. Median overall survival was 20.5 months (95% CI, 16.7–25.0 month) in the TTFiels and temozolomide and 15.6 months (95% CI, 13.3–19.1 months) in the temozolomide arm with HR 0.64 (99.4% CI, 0.42–0.98, $p = 0.04$). There were similar adverse events between the two arms with the exception of localized skin toxicity with 45% of patients experiencing mild to moderate skin toxicity and 2% grade 3 toxicity. TTField compliance was estimated at 75% of patients enrolled on the TTField arm for more than 75% of the time in the first three months. In October 2015, NovoTTF was approved for patients with newly diagnosed glioblastoma along with temozolomide.

NovoTTF—Relapsed Glioblastoma

Stupp et al. conducted the first randomized clinical trial with NovoTTFields in patients with relapsed glioblastoma. Patients were randomized 1:1 to receive either TTFields or salvage chemotherapy of physician choice. 120 patients were randomized to receive TTFields, but only 93 patients (78%) completed >4 weeks of treatment. Median compliance in the TTF group was approximately 86% and the average daily use of TTF was 20.6 h. 117 patients were enrolled and 113 patients received salvage chemotherapy as determined by a local oncologist. In the end, there was no improvement in survival seen; however, TTfields did not appear to be inferior to the chemotherapy arm. The results of this trial led to the approval of NovoTTFields for patients with relapsed glioblastoma in March 2011 [39].

Conclusions

Despite significant advances over the last two decades, a comprehensive understanding of the molecular underpinnings of malignant glioma and the impact on clinical management is still a long way off. Increasingly, the predictive power of mgmt methylation, 1p/19q deletion, and IDH1 mutational status are being incorporated into day-to-day treatment decision making for patients with malignant glioma; however, as yet undiscovered molecular features and the implication of these findings will likely lead to more effective treatment in the future. Although as this review has illustrated there are some reasonable treatment options for patients with malignant glioma, the hope is that one day we will employ an understanding of the complex genetics of these tumors to define diagnosis, treatment, and clinical trial design.

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