Minireview

Temozolomide and Treatment of Malignant Glioma

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Abstract

Malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) occur more frequently than other types of primary central nervous system tumors, having a combined incidence of 5–8/100,000 population. Even with aggressive treatment using surgery, radiation, and chemotherapy, median reported survival is less than 1 year. Temozolomide, a new drug, has shown promise in treating malignant gliomas and other difficult-to-treat tumors.

Temozolomide, a p.o. imidazotetrazine second-generation alkylating agent, is the leading compound in a new class of chemotherapeutic agents that enter the cerebrospinal fluid and do not require hepatic metabolism for activation. In vitro, temozolomide has demonstrated schedule-dependent antitumor activity against highly resistant malignancies, including high-grade glioma. In clinical studies, temozolomide consistently demonstrates reproducible linear pharmacokinetics with approximately 100% p.o. bioavailability, noncumulative minimal myelosuppression that is rapidly reversible, and activity against a variety of solid tumors in both children and adults. Preclinical studies have evaluated the combination of temozolomide with other alkylating agents and inhibitors of the DNA repair protein O6-alkylguanine alkyltransferase to overcome resistance to chemotherapy in malignant glioma and malignant metastatic melanoma. Temozolomide has recently been approved in the United States for the treatment of adult patients with refractory anaplastic astrocytoma and, in the European Union, for treatment of glioblastoma multiforme showing progression or recurrence after standard therapy. Predictable bioavailability and minimal toxicity make temozolomide a candidate for a wide range of clinical testing to evaluate the potential of combination treatments in different tumor types. An overview of the mechanism of action of temozolomide and a summary of results from clinical trials in malignant glioma are presented here.

Introduction

Malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) occur more frequently than other types of primary CNS tumors, having a combined incidence of 5–8/100,000 population. Even with aggressive treatment using surgery, radiation, and chemotherapy, median reported survival is less than 1 year (1). Temozolomide, a new drug, has shown promise in treating malignant gliomas and other difficult-to-treat tumors. Temozolomide represents a new class of second-generation imidazotetrazine prodrugs that undergo spontaneous conversion under physiological conditions to the active alkylating agent MTIC. Thus, temozolomide does not require hepatic metabolism for activation (2).

Interest in temozolomide as an antitumor agent derives from its broad-spectrum antitumor activity in tumor models in mice (3). In vitro, temozolomide has demonstrated schedule-dependent antitumor activity against a variety of malignancies, including glioma, metastatic melanoma, and other difficult-to-treat cancers (3–5). In preclinical studies, temozolomide demonstrated distribution to all tissues, including penetration into the CNS; relatively low toxicity compared with its parent compound, mitozolomide; and antitumor activity against a broad range of tumor types, including glioma, melanoma, mesothelioma, sarcoma, lymphoma, leukemia, and carcinoma of the colon and ovary (3–8). Its demonstrated ability to cross the blood-brain barrier is of special interest with respect to its activity in CNS tumors (9).

In Phase 1 and 2 clinical studies conducted by the CRC (London, United Kingdom), temozolomide was absorbed rapidly, exhibited 100% p.o. bioavailability within 1–2 h of administration, and demonstrated antineoplastic activity in recurrent high-grade glioma, melanoma, and mycosis fungoides (10–13). Results of these trials showed that when temozolomide is administered p.o. once daily for 5 days in a 4-week cycle, it is well tolerated, producing mild-to-moderate toxicity that is both predictable and easily managed. The results also confirmed the ability of temozolomide to penetrate the CNS and indicated that temozolomide has considerable potential in treating gliomas and improving the QOL of patients with glioma (12–14). Additional Phase 1 studies have confirmed these results and have extended these observations to pediatric patients (15, 16).

Temozolomide has been evaluated in a number of Phase 2

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Abbreviations used: MTIC, 5-(3-methyltriazen-1-yl)imidazole-4-carboxamide; DTIC, 5-(3,3-dimethyl-1-triazeno)imidazole-4-carboxamide, or dacarbazine; CNS, central nervous system; CRC, Cancer Research Campaign; BCNU, carmustine; AIC, 5-aminomidazole-4-carboxamide; O6-MG, O6-methylguanine; AGT, alkylguanine alkyltransferase; CCNU, lomustine; PARP, poly(ADP)-ribose polymerase; O6-BG, O6-benzylguanine; AUC, area under the concentration-time curve; MTD, maximum tolerated dose/dosage; CT, computerized tomography; PK, pharmacokinetic(s); CR, complete response; PR, partial response; QOL, quality of life; FDA, United States Food and Drug Administration; MMR, mismatch repair; DLT, dose-limiting toxicity; PFS, progression-free survival; CI, confidence interval.
and 3 clinical trials for the treatment of glioblastoma multiforme, anaplastic astrocytoma, and malignant metastatic melanoma—malignancies for which there are no satisfactory therapies. On the basis of the results of these studies, temozolomide has been approved in the European Union for the treatment of patients with glioblastoma multiforme showing progression or recurrence after standard therapy. Recently, temozolomide received accelerated approval from the FDA for treatment of adult patients with anaplastic astrocytoma who have relapsed after treatment that included a nitrosourea drug (BCNU or CCNU) and procarbazine. Studies are under way to evaluate the combination of temozolomide with other chemotherapeutic agents and biochemotherapy in the treatment of malignant glioma and metastatic melanoma, respectively. This article reviews the mechanism of action of temozolomide as an anticancer agent and summarizes the most recent clinical studies of temozolomide for the treatment of malignant gliomas.

**Background**

Temozolomide was synthesized at Aston University in the early 1980s as one of a series of novel imidazotetrazinones (17). These agents were structurally unique because they contained three adjacent nitrogen atoms that conferred unique physicochemical properties and much greater antitumor activity than the previously synthesized bicyclic triazenes, which contained only two adjacent nitrogen atoms (17). The most potent antitumor compound of this class of compounds, mitozolomide, showed potent antitumor activity against a large panel of murine tumors (18). Mitozolomide is a produg that spontaneously decomposes to a highly reactive DNA-cross-linking metabolite without any need for metabolic activation (19–23). Although Phase 1 clinical studies of mitozolomide revealed some activity against small-cell carcinoma of the lung and malignant melanoma, it also produced unpredictable and severe thrombocytopenia that limited its usefulness (24). These preliminary results precluded further clinical development of mitozolomide.

Temozolomide, a 3-methyl derivative of mitozolomide, was less toxic than mitozolomide and exhibited comparable antitumor activity against various murine tumors (3). Additional characteristics that justified its further development for clinical evaluation in patients with cancer included wide tissue distribution with penetration into the intact mouse brain (25), 100% bioavailability after p.o. dosing, and no requirement for enzymatic conversion to the potent antitumor metabolite MTIC.

**Mechanism of Action**

The methylation of DNA seems to be the principal mechanism responsible for the cytotoxicity of temozolomide to malignant cells. The spontaneous conversion of temozolomide to the reactive methylating agent MTIC is initiated by the effect of water at the highly electropositive C3 position of temozolomide. This activity opens the ring, releases CO2, and generates MTIC (Fig. 1). The initial proposal was that this effect of water was catalyzed in the close environment of the major groove of DNA (26, 27), but confirming this mechanism has been difficult, and it is known that temozolomide converts readily to MTIC in free solution in the absence of DNA (2). MTIC degrades to the methyldiazonium cation, which transfers the methyl group to DNA and to the final degradation product, AIC, which is excreted via the kidneys (28, 29). The methyldiazonium cation can also react with RNA and with soluble and cellular protein (23). However, the methylation of RNA and the methylation or carboxylation of protein do not appear to have any known significant role in the antitumor activity of temozolomide. Additional studies are required to clarify the role of these targets in the biochemical mechanism of action of temozolomide.

The spontaneous conversion of temozolomide to MTIC is dependent on pH. Comparison of the half-life of temozolomide in phosphate buffer [pH 7.4] t1/2 = 1.83 h; Refs. 28, 29] with the mean plasma half-life observed in patients after i.v. and p.o. dosing (t1/2 = 1.81 h; Refs. 10, 29) indicates that the conversion of temozolomide to MTIC is a chemically controlled reaction with little or no enzymatic component. The nonenzymatic conversion of temozolomide to MTIC may contribute to its highly reproducible PK in comparison with that of other alkylating agents such as DTIC and procarbazine, which must undergo metabolic conversion in the liver and are, thus, subject to interpatient variation in rates of conversion (27, 29).

Among the lesions produced in DNA after treatment of cells with temozolomide, the most common is methylation at the N7 position of guanine, followed by methylation at the O6 position of adenine and the O6 position of guanine (29). Although both the N7-methylguanine and O6-methyladenine adducts probably contribute to the antitumor activity of temozolomide in some if not all sensitive cells, their role is controversial (30–32). The O6-MG adduct (which accounts for 5% of the total adducts formed by temozolomide; Ref. 29) probably plays a critical role in the antitumor activity of the agent. This is supported by the correlation between the sensitivity of tumor cell lines to temozolomide and the activity of the DNA repair protein O6-alkylguanine alkyltransferase, which specifically removes alkyl groups at the O6 position of guanine. Cell lines that have low levels of AGT are sensitive to the cytotoxicity of temozolomide, whereas cell lines that have high levels of this repair protein are much more resistant to it (33–35). This correlation has also been observed in human glioblastoma xenograft models (4, 5, 8). The preferential alkylation of...
guanine and adenine and the correlation of sensitivity to the drug with the ability to repair the O^6^-alkylguanine lesion also have been seen with triazine, DTIC, and the nitrosourea alkylating agents BCNU and CCNU (35–37).

The cytotoxic mechanism of temozolomide appears to be related to the failure of the DNA MMR system to find a complementary base for methylated guanine. This system involves the formation of a complex of proteins that recognize, bind to, and remove methylated guanine (38–40). The proposed hypothesis is that when this repair process is targeted to the DNA strand opposite the O^6^-MG, it cannot find a correct partner, thus resulting in long-lived nicks in the DNA (41). These nicks accumulate and persist into the subsequent cell cycle, where they ultimately inhibit initiation of replication in the daughter cells, blocking the cell cycle at the G2-M boundary (41–44). In both murine (42) and human (45) leukemia cells, sensitivity to temozolomide correlates with increased fragmentation of DNA and apoptotic cell death. In addition to causing cell death, there is evidence from preclinical studies that DNA adducts formed by temozolomide and the subsequent alteration of specific genes and their cognate protein products may reduce the metastatic potential of tumor cells by altering the immunogenicity of the tumor cells (46–48). It has also been postulated that temozolomide-induced DNA damage and subsequent cell-cycle arrest may reduce the metastatic properties of some tumor cells (49–51).

Mechanisms of Resistance

**AGT.** The two primary mechanisms of resistance for temozolomide and other alkylating agents are the enzyme AGT (52, 53) and a deficiency in the MMR pathway. Of these two mechanisms, AGT plays a primary role in resistance to temozolomide by removing the alkyl groups from the O^6^ position of guanine, in effect reversing the cytotoxic lesion of temozolomide (54). The sensitivity of tumor cell lines to temozolomide and the alkylating agents BCNU and DTIC can be correlated with AGT levels (37, 45, 55–58). Furthermore, retrovirus-mediated transfer of human AGT gene to cells that are devoid of endogenous AGT activity confers a high level of resistance on temozolomide and other methylating and chloroethylating agents (59).

**MMR Pathway.** Although AGT is clearly important in the resistance of cells to temozolomide, some cell lines that express low levels of AGT are nevertheless resistant, which indicates that other mechanisms for resistance may be involved (60, 61). A deficiency in the MMR pathway resulting from mutations in any one or more of the five or six protein complexes that recognize and repair DNA can render cells tolerant to methylation and to the cytotoxic effects of temozolomide. This deficiency in the MMR pathway results in a failure to recognize and repair the O^6^-MG adducts produced by temozolomide and other methylating agents (33, 62, 63). DNA replication continues past the O^6^-MG adducts without cell cycle arrest or apoptosis. Resistance in tumor cells that are deficient in MMR is unrelated to the level of AGT and is, therefore, unaffected by AGT inhibitors.

**PARP.** Another possible mechanism of resistance for temozolomide is the base excision repair pathway. Studies have shown that treatment of human tumor cells with temozolomide induced an increase in the activity of PARP, which is believed to be involved in nucleotide excision repair (64, 65), and the inhibition of PARP has been reported to enhance the cytotoxicity of methylating agents (66–68). Several studies with inhibitors of PARP and with cell lines deficient in either MMR or excision repair have indicated a role of the repair of N^7^-methylguanine and O^3^-methyladenine adducts in the resistance to the antitumor activity of temozolomide and other alkylating agents (30, 33, 66, 67). However, the importance of these adducts in the antitumor activity of the drug may be secondary to that of the O^6^-MG adduct, except in those tumors that are deficient in base excision repair (31, 32, 69).

Reducing Resistance to Temozolomide

**Alkylating Agents.** Several preclinical studies have examined methods for reducing the resistance to alkylating agents such as temozolomide. Agents that deplete AGT levels or inhibit the activity of the excision-repair pathway reduce resistance to temozolomide. Other than those mentioned above, few studies have investigated the use of agents that inhibit the excision-repair pathway, but various studies (5) have used combinations of different alkylating agents to deplete AGT levels. Additive or more than additive antitumor effects and complementary toxicity profiles characterized these combinations. Because it has a mild toxicity profile and the ability to deplete AGT, temozolomide has the potential to combine with other alkylating agents such as BCNU, assuming that overlapping toxicities are manageable (5).

**O^6^-BG.** O^6^-BG is a low-molecular-weight substrate for AGT and a potent inhibitor of AGT-mediated resistance to DNA damage by chloroethylnitrosoureas and methylating agents (36, 70, 71). Evidence from preclinical studies suggests a role for O^6^-BG in increasing the therapeutic index of temozolomide. Pretreatment with O^6^-BG enhances the activity of temozolomide in vitro and in vivo in tumor cells that have high levels of AGT but has little effect on tumor cells that have low or undetectable levels of AGT (8, 33, 34, 56, 72). However, in vivo enhancement of temozolomide activity by O^6^-BG has been observed in a human glioma xenograft derived from a low-AGT-producing cell line that is refractory to O^6^-BG enhancement of temozolomide activity in vitro (73), which suggests that some in vivo metabolic interaction with O^6^-BG enhanced the activity of temozolomide. In these studies, extended treatments with O^6^-BG are more effective than single treatments (56, 73). In a human melanoma xenograft model, a combination of O^6^-BG and temozolomide, given on a 5-day schedule, resulted in a greater antitumor effect than did an equitoxic dose of temozolomide (8). The combination of temozolomide and O^6^-BG also resulted in a delay of tumor growth equivalent to that produced by a 3-fold greater dose of temozolomide on the same 5-day schedule.

Other studies have shown that bone marrow cells are low in AGT activity, and AGT depletion with O^6^-BG substantially increased the sensitivity of these cells to O^6^-alkylating agents including BCNU and temozolomide (74–76). It is, thus, possible that hematological toxicity may limit the doses of O^6^-BG and other inhibitors of DNA repair used in clinical practice. A
study of the effect of O\textsuperscript{6}-BG pretreatment on the toxic and clastogenic effects of temozolomide on murine hematopoietic cells in vivo has confirmed potentiation of bone marrow cell sensitivity (75). An increase in the frequency of formation of micronuclei in the bone marrow of mice pretreated with O\textsuperscript{6}-BG observed in this study also suggests the possibility of an increased incidence of secondary leukemias.

Attempts to reduce the toxicity produced by this combination have focused on protection of normal hematopoietic tissue by transducing hematopoietic progenitor cells with O\textsuperscript{6}-BG-resistant methyltransferase genes (77, 78, 79). Expression of a double-mutant form of AGT in murine bone marrow cells significantly reduced the toxicity produced by temozolomide given in combination with O\textsuperscript{6}-BG and led to a reduction in the frequency of combined O\textsuperscript{6}-BG/temozolomide-induced micronuclei in the bone marrow (78). Although transducing hematopoietic progenitor cells with O\textsuperscript{6}-BG-resistant methyltransferase genes committed murine hematopoietic progenitors against the toxicity of O\textsuperscript{6}-alkylating agents, a similar effect is not observed with primitive, multipotent spleen colony-forming cells (76). In a recent study, Chinnasamy et al. (76) showed that transduction of primitive, multipotent spleen colony-forming cells with a double mutant of AGT did not result in a significant protection against the toxicity produced by combination of BCNU and O\textsuperscript{6}-BG. These results indicate that the protective effect afforded by transducing hematopoietic progenitor cells with O\textsuperscript{6}-BG-resistant methyltransferase genes may be highly specific to the cytotoxic agent and the cell type involved (76). Thus, further investigation is needed to define the potential clinical benefit of this type of protective genetic therapy.

**Clinical Experience with Temozolomide in Malignant Gliomas**

**Initial Phase 1 Studies.** The safety, PK, and antitumor activity of temozolomide were initially evaluated in a Phase 1 trial sponsored by the CRC (10). In this study, 51 patients with advanced cancer received a single p.o. dose of temozolomide. The absolute bioavailability of temozolomide was also studied in five of these patients. Temozolomide demonstrated approximately 100% p.o. bioavailability after i.v. versus p.o. administration. Peak plasma concentrations occurred within 0.33–2 h after p.o. administration, and the AUC increased linearly with the dose. Elimination was equally rapid, with a plasma half-life ranging from 1.6 to 1.8 h and a whole-body clearance of 12 liters/h. The PK of temozolomide was linear and reproducible, with little interpatient variation. PK parameters did not vary between the first and fifth dose, which indicated that temozolomide did not accumulate after multiple doses (10).

On the basis of the schedule-dependent antitumor activity observed with temozolomide in preclinical studies (3), an additional 42 patients were given a single p.o. dose of temozolomide started at 150 mg/m\textsuperscript{2} and escalated to 240 mg/m\textsuperscript{2} for 5 days in a 4-week cycle if no major myelosuppression was detected. In this population, the DLT of temozolomide was mild-to-moderate myelosuppression (neutropenia and thrombocytopenia), which was both predictable and easily controlled. The MTD was 200 mg/m\textsuperscript{2} per day (10). As a result, the recommended dosage for Phase 2 studies was 150 mg/m\textsuperscript{2} for the first course and, in the absence of any major myelosuppression, escalation to 200 mg/m\textsuperscript{2} for subsequent courses. Nonhematological toxicity, mainly nausea and vomiting, was mild and controlled with standard antiemetic agents. No drug-related adverse CNS effects or alopecia occurred with temozolomide (10).

Subsequent Phase 1 studies have been conducted to evaluate the safety of a machine-filled capsule preparation of temozolomide, which differed from the hand-filled preparation used in the initial CRC Phase 1 study (80, 81–84).

These studies have confirmed the safety, tolerability, and PK of temozolomide reported by Newlands et al. (10).

**Safety.** Consistent with the results of a Phase 1 study, hematological toxicity, specifically thrombocytopenia and neutropenia, was dose limiting. Neutropenia or thrombocytopenia typically appeared 21–28 days after the first dose of each cycle and recovered to grade 1 myelosuppression within 7–14 days. Grade 4 toxicity occurred at cumulative p.o. dosages of more than 1000 mg/m\textsuperscript{2} over 5 days, but little other significant toxicity was seen. Grades 3 or 4 myelosuppression generally occurred in fewer than 10% of patients studied.

Prior treatment with chemotherapy, radiation, or both has a significant effect on the MTD of temozolomide (83). Hammond et al. (80) evaluated the effect of prior myelosuppressive therapy on toxicity and PK profile of temozolomide in 24 advanced cancer patients who were stratified according to prior exposure to chemotherapy and radiation. Patients in either category received a dosage of 100 mg/m\textsuperscript{2}/day temozolomide for 5 days, which was escalated to 150 and 200 mg/m\textsuperscript{2}/day in the absence of myelosuppression (80). The MTD for temozolomide was established as 150 mg/m\textsuperscript{2}/day. Another similar Phase 1 study, reported by the National Cancer Institute, evaluated the safety of temozolomide in patients who were stratified on the basis of prior exposure to nitrosourea (83). The MTD for patients with prior exposure to nitrosourea was 150 mg/m\textsuperscript{2}/day, and the MTD for patients without such prior exposure was 250 mg/m\textsuperscript{2}/day. An evaluation of the PK of temozolomide showed that clearance from the plasma was significantly less in patients with prior exposure to nitrosourea than it was in patients without such prior exposure (83). This may have contributed to the lower dosage of temozolomide that was tolerated by these patients and had a notable effect on the dosing recommendation for these patients.

The results of these studies indicate that a dosage of 200 mg/m\textsuperscript{2} of temozolomide given on a 5-day schedule repeated every 28 days is appropriate for patients who are not pretreated with radiation, chemotherapy, or both. Patients who are pretreated with chemotherapy receive a lower starting dosage of temozolomide (i.e., 150 mg/m\textsuperscript{2}), which can be escalated to 200 mg/m\textsuperscript{2} in subsequent courses in the absence of grade 3 or 4 myelosuppression (80). A summary of the administration schedule for temozolomide and the MTD that was observed in several completed Phase 1 trials is presented in Table 1.

**PK.** PK analysis of temozolomide has consistently shown that the PK of temozolomide are linear, with 100% bioavailability after p.o. administration, and that there is no accumulation of drug on day 5 after 5 days of dosing. Time to maximum plasma concentration ($t_{\text{max}}$) is approximately 1 h. Elimination half-life ($t_{1/2}$) is 1.6–1.8 h. A summary of the PK properties of temozolomide in adults is given in Table 2.
Studies with p.o. 14C-temozolomide in patients with advanced cancer (82) indicate that the primary pathway for its clearance from plasma is degradation to MTIC with further degradation to AIC. In these studies, temozolomide was eliminated primarily in the urine, with 36% of the dose excreted as the intact drug and AIC. The effect of gastric pH and ingestion of food on the PK properties and p.o. bioavailability of temozolomide has also been evaluated (85). Beale et al. (85) evaluated the effect of an increase in gastric pH, through the use of ranitidine, on the p.o. bioavailability and plasma PK of temozolomide and MTIC. In this study, the p.o. bioavailability, maximum plasma concentration, and half-life of temozolomide were not affected by an increase in gastric pH of 1 to 2 units, resulting from the administration of ranitidine every 12 h on either the first 2 or the last 2 days of the 5-day temozolomide dosing schedule (85). Administration of temozolomide after ingestion of food results in a small decrease in p.o. availability (84). When temozolomide was taken after a meal, a slight but statistically significant reduction (9%) occurred in the rate and extent of absorption. Because AUC confidence limits were within the bioequivalence guidelines of 80–125%, it is unlikely that this reduction has any clinical effect on the antitumor activity of temozolomide (84). Because bioavailability and 14C-temozolomide metabolism studies have shown that p.o. bioavailability is essentially complete (82), the p.o. formulation of the drug has been used for clinical studies.

**Pediatric Patients.** Phase 1 studies of temozolomide were expanded to include pediatric cancer patients (16). In a Phase 1 study conducted to define the multiple-dose PK of temozolomide, 20 patients between 3 and 17 years old were given temozolomide over a dosage range of 100–240 mg/m²/day (15). Patients were stratified according to prior craniospinal irradiation or nitrosourea therapy. The MTD was 200 mg/m² for patients who had not received prior craniospinal irradiation or nitrosourea therapy but was not defined for children with prior craniospinal irradiation because of the small number of patients. Temozolomide was absorbed rapidly, had an AUC that increased in a dosage-related manner, and showed no evidence of accumulation. The plasma half-life, whole-body clearance, and volume of distribution were independent of dosage (Table 3). Compared with adult patients treated with 200 mg/m²/day, children seemed to have a higher AUC (48.7 versus 34.5 μg·h/ml), most likely because children have a larger ratio of body surface area to volume (15). Despite higher concentrations at dosages equivalent to those used in adult patients, the bone marrow function in pediatric patients appears to allow greater exposure to the drug before bone marrow DLT develops.

**Antitumor Activity.** As predicted by preclinical evaluations (5), Phase 1 studies have demonstrated the antitumor activity of temozolomide in a number of difficult-to-treat cancers for which there is no satisfactory treatment. In the CRC Phase 1 study (10), clinical responses were observed in patients with recurrent high-grade glioma, melanoma, and mycosis fungoides. Similar antitumor activity has also been observed in subsequent Phase 1 trials conducted with machine-filled capsules. In these studies, temozolomide demonstrated clinical activity against high-grade gliomas in both adult and pediatric patients (84).

**Phase 2 and 3 Clinical Experience**

**Rationale.** Adjuvant chemotherapy with single-agent nitrosourea or combination therapy for the treatment of recurrent malignant glioma and malignant melanoma is far from satisfactory. This is primarily attributable to the de novo or acquired resistance to chemotherapeutic agents (86). Although alkylating agents such as procarbazine have activity in the treatment of malignant glioma, the use of these agents has been associated with a high level of toxicity and only a modest improvement in overall survival rate (87–89). As a result, there is a need for new
agents that are effective and can be used in combination with other agents or radiation to overcome resistance. The acceptable safety profile and clinical activity of temozolomide observed in patients with malignant glioma and recurrent astrocytoma prompted subsequent Phase 2 and 3 studies to confirm the activity of temozolomide in these malignancies. The CRC has conducted a number of these studies, in which the activity of temozolomide in recurrent and newly diagnosed gliomas was established. A summary of Phase 2 and 3 trials is presented in Table 4.

**Primary Brain Tumors.** O’Reilly et al. (12) treated 28 patients with primary brain tumors. The initial dosage of 150 mg/m²/day of temozolomide was given p.o. once daily for 5 days; this dosage was increased to 200 mg/m²/day once daily for 5 days and repeated at 28-day intervals if the patient did not experience significant myelosuppression at day 22 of the first cycle. Treatment was well tolerated. Grade 3 leukopenia occurred in only 3 (5%) of 57 courses, and grade 3 thrombocytopenia was reported in only 4 (7%) of 57 courses. Of the 10 evaluable patients with recurrent astrocytoma after radiation therapy, 5 showed major improvement on CT and complete resolution of clinical signs and symptoms that persisted for 3–6 months; 3 other patients showed a slight reduction or no change on CT, although their neurological condition improved (12). Major improvement on CT also was reported for two of nine evaluable patients treated with two courses of temozolomide before cranial irradiation for newly diagnosed high-grade astrocytomas; two others showed slight improvement. Three additional evaluable patients with primary brain tumors, including one with recurrent medulloblastoma after chemotherapy and radiation therapy, experienced major improvement on CT that was maintained for 6 months (12). This study was extended to 75 patients—48 with recurrent disease and 27 with new diagnoses (90). Improvements on CT were seen in 12 (25%) of the patients with recurrent disease and in eight (30%) of the patients with new diagnoses. Twenty-two % of patients with recurrences and 43% of those with newly diagnosed tumors survived to 1 year. Although there was a clear improvement in the QOL in respond-ers who used the 5-day schedule, no conclusions could be reached about the effect on extended survival benefit in comparison with the overall survival data established by historical results (90). This study confirmed, however, the activity of temozolomide against gliomas in patients who have failed to respond to intensive radiation therapy.

Similar results were reported in a multicenter Phase 2 study conducted by the CRC that evaluated temozolomide in patients diagnosed with anaplastic astrocytoma, glioblastoma multiforme (grade 4), and unclassified high-grade astrocytoma (grades 3–4; 13). In this study, objective responses, measured by improvement in neurological status, were seen in 11 (11%) of 103 patients who received temozolomide; 5 of these patients had improvement on CT or magnetic resonance imaging scans (13). An additional 47% of the patients in the study had stable disease. The median survival of all patients with measurable response was 5.8 months, and 22% of the patients had no neurological or radiological evidence of progressive disease at 6 months. The results of this study further confirmed the activity of temozolomide in patients with recurrent and progressive high-grade glioma.

Recently, three open-label, multi-institutional studies have evaluated the use of temozolomide in 525 patients with malignant glioma. These studies represent the largest evaluation of a single agent in patients with recurrent malignant gliomas that were rigorously controlled with strict prospectively defined criteria for assessment of tumor response, central review of histology, and validated instruments to assess health-related QOL. The first two trials evaluated the safety, efficacy, and health-related QOL effects of temozolomide in patients with glioblastoma multiforme at first relapse and were as follows: (a) pivotal multicenter Phase 2 study that compared the PFS at 6 months and the safety in patients treated with temozolomide with those in patients treated with procarbazine (91); and (b) a second supportive trial in patients with glioblastoma multiforme to further examine the efficacy and health-related QOL aspects of temozolomide. In the pivotal Phase 2 study, 225 patients were randomized to receive either temozolomide (n = 112) or procarbazine (n = 113; Ref. 91). The treatment arms were similar with respect to baseline disease characteristics and prior therapies. Objective responses (PR or stable disease) were seen in 46% of patients treated with temozolomide and in 33% of patients treated with procarbazine, with PRs occurring in 5% of patients in both groups (91). Patients treated with temozolomide had significantly better 6-month PFS and overall survival than those treated with procarbazine (21% in the temozolomide group versus 9% in the procarbazine group; P = 0.008). Median PFS was also better for temozolomide compared with procarbazine (2.89 months for temozolomide versus 1.97 months for procarbazine; hazard ratio of 1.47; P = 0.0063; Ref. 91. A

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**Table 3** PK parameters in pediatric patients

<table>
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<th>Parameter</th>
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<tr>
<td>Tmax (h)</td>
<td>1.27 75</td>
<td>1.43 36</td>
<td>1.9 53</td>
<td>1.9 40</td>
<td>1.7 46</td>
</tr>
<tr>
<td>AUC (µg·h/ml)</td>
<td>23.0 11</td>
<td>27 19</td>
<td>37 2</td>
<td>48 17</td>
<td>45 16</td>
</tr>
<tr>
<td>t1/2 (h)</td>
<td>1.7 11</td>
<td>1.7 9</td>
<td>1.7 8</td>
<td>1.7 4</td>
<td>1.4 22</td>
</tr>
<tr>
<td>CL/F (ml/min)</td>
<td>68.6 42</td>
<td>97 36</td>
<td>68 9</td>
<td>71 29</td>
<td>117 35</td>
</tr>
<tr>
<td>Vd/F (l)</td>
<td>10.5 55</td>
<td>13.9 29</td>
<td>10.4 16</td>
<td>10.5 30</td>
<td>13.6 43</td>
</tr>
</tbody>
</table>

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<sup>b</sup> CV, coefficient of variation.

Reprinted with permission from Estlin, et al. (15).
difference in PFS in favor of temozolomide was observed as early as 1 month after randomization, and the difference was maintained for several months (Fig. 2). Similar findings were observed in the confirmatory single-arm study that evaluated temozolomide in 138 glioblastoma multiforme patients. In this study, treatment with temozolomide resulted in a PFS of 19% (95% CI, 12–26%; Table 5). These studies formed the basis for the approval of temozolomide in the European Union for the treatment of patients with glioblastoma multiforme showing progression or recurrence after standard therapy.

Table 4  Phase 2 and 3 trials of temozolomide in malignant glioma

<table>
<thead>
<tr>
<th>Study</th>
<th>Pathology</th>
<th>Dosing schedule</th>
<th>Enrollment</th>
<th>Response</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>O’Reilly (12)</td>
<td>Primary brain tumors</td>
<td>150 mg/m²/day p.o. for 5 days (total dose, 750 mg/m²); escalated to 200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days</td>
<td>28</td>
<td>CT response in 5/10 recurrent AA (50%) and 4/7 neoadjuvant AA (57%)</td>
<td>Improved CT, neurological signs/symptoms of 3–6 mo duration</td>
</tr>
<tr>
<td>Newlands (116) (90)</td>
<td>AA, GBM</td>
<td>150 mg/m²/day p.o. for 5 days (total dose, 750 mg/m²); escalated to 200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days</td>
<td>75 (48 recurrent, 27 neoadjuvant)</td>
<td>12 PR (25%); 8 PR (30%)</td>
<td>Survival advantage not shown</td>
</tr>
<tr>
<td>Bower (13)</td>
<td>Progressive or recurrent AA, GBM</td>
<td>200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days</td>
<td>103</td>
<td>11 (11%) objective response</td>
<td>48 (47%) stable disease; median response, 4.6 mo</td>
</tr>
<tr>
<td>Yung (91)</td>
<td>GBM at first relapse</td>
<td>Temozolomide: 150 mg/m²/day p.o. for 5 days (total dose, 750 mg/m²); escalated to 200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days. Procarbazine: 150 mg/m²/day for 28 days every 56 days</td>
<td>225</td>
<td>Temozolomide; PR (5.4%); SD (40.2%); PR, or SD (45.6%)</td>
<td>Temozolomide, PFS; 21% at 6 mo; median, 2.89 mo</td>
</tr>
<tr>
<td>Yung (92)</td>
<td>AA at first relapse</td>
<td>150 mg/m²/day p.o. for 5 days (total dose, 750 mg/m²); escalated to 200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days</td>
<td>162</td>
<td>13 CR (8%); 57 CR or PR (35%); 101 CR, PR, or stable disease (62%)</td>
<td>PFS: 46% at 6 mo; 24% at 12 mo</td>
</tr>
<tr>
<td>Friedman (93)</td>
<td>Newly diagnosed GBM, AA</td>
<td>200 mg/m²/day p.o. for 5 days (total dose, 1000 mg/m²); every 28 days</td>
<td>38 (33 GBM, 5 AA)</td>
<td>3 CR (9%); 14 PR (43%)</td>
<td>Median overall survival, 13.6 mo</td>
</tr>
</tbody>
</table>

* Numbers in parentheses are the reference sources for the data.

AA, anaplastic astrocytoma; GBM, glioblastoma multiforme; OS, overall survival.

111 were confirmed to have had anaplastic astrocytoma or anaplastic mixed oligoastrocytoma. Patients who had not been previously treated with chemotherapy received a starting dosage of 200 mg/m² of p.o. temozolomide daily for 5 days on a 28-day cycle; patients with a history of chemotherapy received a reduced dose of 150 mg/m²/day, which was increased in subsequent cycles if no grade 3 or 4 hematological toxicities occurred. Pathology confirmation of the diagnosis, including central review of histology, was required in all patients. In the intent-to-treat population, PFS at 6 months was 46%, and the median time to progression was 5.4 months (Table 6). The median overall survival was 13.6 months, and the 6- and 12-month survival rates based on Kaplan-Meier estimates were 75% (95% CI, 69–83%) and 56% (95% CI, 50–66%), respectively (92).
Temozolomide in Malignant Glioma

with anti-AGT antibody, there were 1 patient with PR, 2 with interest that in 11 tumors that had 20% or more cells staining PR. One patient with anaplastic astrocytoma had a PR. It is of glioblastoma multiforme, 3 achieved a CR and 14 achieved a were observed in 47% of the patients. Among the patients with for 5 days on a 28-day cycle. Responses (complete and partial) with a starting dosage of 200 mg/m2 of p.o. temozolomide daily

metastatic melanoma, including patients with brain metastases (11). Fifty-six patients were given p.o. temozolomide 150 mg/m2 /day) were administered at 28-day intervals. Among the patients, and no grade 4 nonhematological toxicity was observed (93). These results suggest that temozolomide has activity in newly diagnosed malignant glioma, and that the evaluation of AGT protein expression may identify individuals who are more likely to respond to temozolomide therapy for malignant glioma.

Malignant Metastatic Melanoma. The efficacy of te-mozolomide was evaluated in a study of patients with advanced metastatic melanoma, including patients with brain metastases (11). Fifty-six patients were given p.o. temozolomide 150 mg/m2 once daily for 5 days. If grade 2 or greater myelosuppression did not occur by day 22, subsequent 5-day courses (200 mg/m2/day) were administered at 28-day intervals. Among the 56 patients (49 with evaluable lesions), CRs occurred in 3, all with lung metastases only, and PRs occurred in 9, which yielded a response rate of 21%. Stable disease was observed in an additional eight patients. The mean duration of response was 6 months (range, 2.5–18 months), and the median survival times were 14.5 months in responding patients and 4.5 months in nonresponders. Leukopenia was the major toxicity; five cases of grade 4 leukopenia, two cases of grade 4 thrombocytopenia, and no other grade 4 toxic effects occurred in the 55 evaluable patients over 217 courses of treatment. These results confirmed the safety and efficacy of temozolomide in malignant metastatic melanoma that were observed in the Phase 1 study (11).

A second Phase 2 trial in advanced malignant melanoma evaluated the relationship between pretreatment AGT levels in biopsies of cutaneous tumors and involved lymph nodes and clinical response to treatment with temozolomide (94). Among the 50 evaluable patients, there were 3 CRs and 4 PRs for an overall response rate of 14%. Stable disease was observed in an additional six patients. Lymphopenia was the major toxicity, however, with only eight and nine cases of grade 3 or higher neutropenia and thrombocytopenia, respectively. Analysis of the pretreatment AGT levels and clinical response to temozolomide in 33 patients revealed that pretreatment levels of AGT are not predictive of response to temozolomide in melanoma (94).

Recently, a Phase 3 trial compared the overall survival, stable disease, and 8 with disease progression. In 25 tumors that had fewer than 20% AGT-positive cells, there were 3 CRs, 12 PRs, 4 patients with stable disease, and 6 patients with disease progression. Temozolomide was well tolerated, with grades 3 and 4 myelosuppression occurring in only 5% of the patients. Grade 3 nausea and constipation occurred in 13% of the patients, and no grade 4 nonhematological toxicity was observed (93). These results suggest that temozolomide has activity in newly diagnosed malignant glioma, and that the evaluation of AGT protein expression may identify individuals who are more likely to respond to temozolomide therapy for malignant glioma.

The use of temozolomide in the treatment of patients with newly diagnosed malignant glioma has also been evaluated (93). Thirty-three patients with newly diagnosed glioblastoma multiforme and five patients with anaplastic astrocytoma were treated with a starting dosage of 200 mg/m2 of p.o. temozolomide daily for 5 days on a 28-day cycle. Responses (complete and partial) were observed in 47% of the patients. Among the patients with glioblastoma multiforme, 3 achieved a CR and 14 achieved a PR. One patient with anaplastic astrocytoma had a PR. It is of interest that in 11 tumors that had 20% or more cells staining with anti-AGT antibody, there were 1 patient with PR, 2 with

| Table 5 | Progression-free survival and overall survival in GBMa patients treated with temozolomideb |
|---------|-----------------------------------------------|----------------|----------------|
|         | PFS                                           | Randomized     |
| 6 mo (%)| 19                                            | 21             |
| Median (mo) | 2.1                                           | 2.89          |
| Overall survival | 46                                           | 60            |
| 6 mo (%) | 5.4                                           |                |

a GBM, glioblastoma multiforme.  
b Ref. 91.

Table 6 Progression-free survival and overall survival in anaplastic astrocytoma patients treated with temozolomide

<table>
<thead>
<tr>
<th></th>
<th>ITTa</th>
<th>Prior PCV</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 mo (%)</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>12 mo (%)</td>
<td>24</td>
<td>29</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>5.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Overall survival (%)</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>6 mo (%)</td>
<td>56</td>
<td>65</td>
</tr>
<tr>
<td>Median (mo)</td>
<td>13.6</td>
<td>15.9</td>
</tr>
</tbody>
</table>

a ITT, intention to treat; PCV, procarbazine, CCNU, and vincristine.  
b Ref. 92.

Fig. 2 PFS for glioblastoma multiforme patients treated with temozolomide: intention to treat population.
PFS, objective response, and safety of temozolomide and DTIC in 305 patients with advanced metastatic melanoma (95). This study also assessed the health-related QOL and PK of both drugs and their metabolite, MTIC. In this study, patients were randomized to receive either p.o. temozolomide at a starting dose of 200 mg/m2/day for 5 days every 28 days or i.v. DTIC at a starting dose of 250 mg/m2/day for 5 days every 21 days. Median survival in the intent-to-treat population was similar for patients treated with temozolomide or DTIC (7.7 and 6.4 months for temozolomide and DTIC, respectively; a hazard ratio of 1.18). Median PFS was significantly longer for temozolomide (1.9 months) versus DTIC (1.5 months; P = 0.012; hazard ratio = 1.37; CI, 1.07–1.75; Ref. 95). Temozolomide was associated with health-related QOL benefit, with more temozolomide-related patients demonstrating an improvement or maintenance in physical functioning at week 12 compared with those treated with DTIC. PK analysis revealed that systemic exposure (AUC) to the parent drug and the active metabolite MTIC was higher after p.o. temozolomide compared with i.v. DTIC. These results indicate that temozolomide demonstrates efficacy equal to that of DTIC against advanced metastatic melanoma.

Overcoming Resistance

Combining two or more drugs that have different cytotoxic mechanisms or are subject to different mechanisms of resistance can produce additive or synergistic effects. The favorable safety profile of temozolomide allows it to be coadministered with various agents. The antitumor activity of temozolomide is dependent on the level of AGT within the tumor cell. Results from preclinical studies indicate that inhibition of AGT potentiates the activity of temozolomide in several human tumor cell lines (5). Several studies have investigated methods to deplete AGT levels further and increase the antitumor effect of temozolomide in combination therapy with BCNU and different dosing schedules.

Combination with Cisplatin. Preclinical evidence indicates that cisplatin enhances the antitumor activity of temozolomide (96). On the basis of these data and complementary toxicity profiles, a Phase 1 trial of the combination was conducted in 15 patients with advanced cancer (97). In this study, cohorts of three patients received temozolomide daily for 5 days together with cisplatin on day 1 for 4 weeks at the following temozolomide (mg/m2/day) and cisplatin (mg/m2) dose levels: 100/75; 120/75; 200/75; and 200/100. The DLT observed at the highest temozolomide/cisplatin dose level was myelosuppression (neutropenia and thrombocytopenia) and vomiting. The MTDs established in this trial were 200 mg/m2/day for temozolomide and 75 mg/m2 for cisplatin. This combination did not alter the PK or the MTD of temozolomide. The principal nonhematological toxicities consisted of nausea, vomiting, and hearing loss. PR was achieved in 2 of the 14 evaluable patients, one with untreated non-small cell lung cancer and the other with squamous cell carcinoma.

Combination with BCNU. In a Phase 1 study evaluating the combination of BCNU (75 mg/m2) given before or after a 5-day course of temozolomide, no differences between the regimens were seen in the PK of temozolomide or the toxicity of the drugs at the doses used (98). One patient with glioblastoma had a PR that has been maintained for 1 year, and two other patients (one with osteosarcoma and one with uterine carcinosarcoma) have had minor responses. This study is continuing so that the MTD for this combination can be established (98).

Combination with IFN-α-2b. Both temozolomide and IFN-α-2b have demonstrated antitumor activity against melanoma. IFN-α-2b is approved in the United States for postsurgical adjuvant treatment of melanoma with high-risk metastases. It is approved in some European countries for use as monotherapy for the palliative treatment of melanoma. In a Phase 1 study to determine the MTD and DLT, patients with histologically confirmed, surgically incurable metastatic melanoma were treated with 5-course doses of p.o. temozolomide in dosages of 100 or 200 mg/m2/day with continuous s.c. injections of IFN-α-2b three times a week at escalating doses starting at 5 mU/m2 (99). In the cohort treated with 1000 mg/m2 of temozolomide and 5 mU/m2 of IFN-α-2b, two patients developed dose-limiting thrombocytopenia, and one patient developed grade 4 neutropenia. When higher doses of IFN-α-2b (7.5 and 10.0 mU/m2) were combined with 150 mg/m2 of temozolomide, grade 4 hematological toxicity was observed in one of six and one of three patients, respectively. No DLT occurred in patients treated with 750 mg/m2 of temozolomide plus 5 mU/m2 of IFN-α-2b. The MTD was determined as temozolomide 150 mg/m2 and IFN-α-2b 7.5 mU/m2 (99). Antitumor responses were seen in 3 of 12 patients, and stable disease in 4 of 12 patients. These results indicate that this combination when administered at the MTD is well tolerated, and the antitumor activity observed provides the basis for additional studies.

Continuous Dosing Schedule. Because AGT levels may recover within the 24-h interval between individual temozolomide doses in each 5-day cycle, dosing more frequently than once a day for 5 days may improve the response to treatment. A Phase 1 study of 24 patients with recurrent tumors, 17 of which were malignant gliomas (81), examined continuous dosing of temozolomide over a 6- to 7-week period with dosages ranging from 50 to 100 mg/m2/day. This schedule produced a higher cumulative dose of drug than the indicated 5-day schedule and increased the AUC by a factor of 2.1 without producing any hematological DLT. No major toxicity was observed at the dosage level of 75 mg/m2/day (81). Objective responses were reported in patients with high-grade glioma and melanoma, and the overall response rate for the prolonged schedule was 33%. Seven (41%) of 17 glioma patients demonstrated tumor responses. Six of the 17 glioma patients maintained stable disease (81).

Summary and Conclusions

Temozolomide is a new and effective p.o. administered anticancer agent that demonstrates a broad spectrum of activity in various solid tumors and distribution to all tissues, including the brain. It spontaneously converts to an active methylating agent with activity against a number of refractory cancers, including malignant glioma, metastatic melanoma, and other solid tumors. Temozolomide is well tolerated, with minimal myelosuppression that is noncumulative and with nonhemato-
logical toxicity that is easily managed with standard antiemetic agents.

Unique characteristics of stability and solubility allow temozolomide to be absorbed readily and distributed to all tissues with approximately 100% bioavailability after p.o. administration. Thus, temozolomide does not require hepatic metabolism for activation and is capable of penetrating the blood-brain barrier. Temozolomide demonstrates dose-linear PK, is cleared rapidly, and does not accumulate with repeat dosing. Its PK yields little intrasubject or intersubject variability, which is manifested by its predictable clinical tolerance and mild side-effect profile.

Little success has been seen with BCNU, CCNU, or procarbazine used as single-agents or in combination chemotherapy for the treatment of high-grade gliomas; surgery and radiation therapy remain the first-line treatments (87, 100). These agents are severely cytotoxic or poorly tolerated, and resistance develops rapidly, which limits the minimal benefits offered by treatment with these drugs (87). Preliminary clinical studies conducted by the CRC demonstrated that temozolomide has meaningful efficacy and an acceptable safety profile in the treatment of patients with malignant glioma. The results have been confirmed in three open-label multi-institutional studies that represent the largest evaluation of a single agent in patients with recurrent malignant gliomas, using strict prospectively defined criteria for the assessment of tumor response, central review of histology, and validated instruments to assess health-related QOL. Temozolomide has also demonstrated activity in patients with newly diagnosed glioma. The tolerability and ease of administration of temozolomide have particular clinical value for the treatment of pediatric glioma, for which chemotherapy is often the primary modality (87).

Although advanced melanoma is relatively resistant to therapy, several biological response modifiers and cytotoxic agents have been reported to produce objective responses including DTIC, IFN-α-2b, and interleukin 2 (101). The objective response rate for DTIC is 15–20%, and it produces a limited number of durable responses. Although various combination regimens of chemotherapy (e.g., DTIC, tamoxifen) and cytokines (e.g., interleukin 2, IFN-α-2b) have increased the rates of remission and improved response rates as much as 50%, no single agent has improved survival rates compared with those obtained with DTIC alone in patients with metastatic malignant disease (101). Additionally, the chemotherapeutic regimens used to treat metastatic malignant disease are ineffective in brain metastases. Thus, for long-term control of metastatic melanoma to be achieved, agents that are effective against CNS metastases must be used. Temozolomide demonstrates comparable activity to that of DTIC against advanced malignant melanoma and may offer an alternative choice to DTIC because of its ability to penetrate the blood-brain barrier.

In summary, the unique pharmacological profile of temozolomide, its availability as an oral agent, and its documented safety and efficacy supports its potential in the treatment of malignant glioma and malignant melanoma. Future studies will focus on various facets of combination therapy, dose intensification, and dose-finding trials with new dosing schedules. Many tumors including sarcoma, colon, lung, and prostate are resistant to standard chemotherapy, and synergistic or additive activity exhibited by temozolomide in combination with other chemotherapeutic agents (e.g., BCNU, cisplatin) or biological-response modifiers (e.g., IFN-α-2b) has been documented in many of these chemoresistant tumor types. Furthermore, the potential for more predictable toxicity, increased antitumor activity, and activity in CNS metastasis may lead to improved therapeutic index and health-related QOL.

Studies are ongoing in recurrent glioma to explore the standard 5-day temozolomide schedule with other cytotoxic agents including 6-thioguanine (Gliadel; BCNU) wafer as well as cis-retinoic acid. Studies in malignant metastatic melanoma are currently exploring the use of the standard 5-day temozolomide schedule in combination with biochemotherapy regimens. Finally, additional Phase 2 studies are planned to explore the antitumor activity of the standard 5-day temozolomide schedule in combination with antimicrotubule agent taxanes (e.g., paclitaxel, docetaxel); topoisoerase I and II inhibitors (e.g., antitumor antibiotics, camptothecin, topotecan); and the angiogenesis inhibitor, thalidomide.

References


Temozolomide and Treatment of Malignant Glioma

Henry S. Friedman, Tracy Kerby and Hilary Calvert


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