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A phase I factorial design study of dose-dense temozolomide alone and in combination with thalidomide, isotretinoin, and/or celecoxib as postchemoradiation adjuvant therapy for newly diagnosed glioblastoma

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External beam radiation therapy (XRT) with concomitant temozolomide and 6 cycles of adjuvant temozolomide (5/28-day schedule) improves survival in patients with newly diagnosed glioblastoma compared with XRT alone. Studies suggest that dose-dense temozolomide schedules and addition of cytostatic agents may further improve efficacy. This factorial design phase I/II protocol tested dose-dense temozolomide alone and combined with cytostatic agents. Patients with newly diagnosed glioblastoma received fractionated XRT to 60 Gy concomitant with temozolomide (75 mg/m^2/day for 42 days). In the phase I portion, patients with stable disease or radiologic response 1 month after chemoradiation were randomized to adjuvant temozolomide alone (150 mg/m^2/day, 7/14-day schedule) or with doublet combinations of thalidomide (400 mg/day), isotretinoin (100 mg/m^2/day), and/or celecoxib (400 mg twice daily), or all 3 agents. Toxicity was assessed after 4 weeks. Among 54 patients enrolled (median age, 52 years; median Karnofsky performance status, 90), adjuvant treatment was not administered to 12 (22%), primarily because of disease progression ($n = 10$). All combinations were well tolerated. Grade 3/4 lymphopenia developed in 63% of patients, but no related infections occurred. One patient treated with temozolomide plus isotretinoin plus thalidomide had dose-limiting grade 3 fatigue and rash, and 1 patient receiving all 4 agents had dose-limiting grade 4 neutropenia. Venous thrombosis occurred in 7 patients, 4 of whom received thalidomide. From study entry, median survival was 20 months and the 2-year survival rate was 40%. Multiple cytostatic agents can be safely combined with dose-dense temozolomide. The factorial-based phase II portion of this study is currently ongoing.

Keywords: dose-dense, glioblastoma, glioma, radiotherapy, temozolomide.

Long-term survival of patients with malignant gliomas remains poor. Population-based studies estimate that the 3-year survival rate for patients with glioblastoma is 5% or less.[1,2] Conventional treatment for newly diagnosed glioblastoma has traditionally consisted of initial surgical resection followed by fractionated external beam radiation therapy (XRT) with or without chemotherapy, usually with regimens containing alkylating agents. However, until recently, the benefit of chemotherapy in this setting remained controversial. Temozolomide, an oral alkylating agent, has

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demonstrated promising activity in several phase II studies in patients with malignant gliomas,[3–5] primarily in the recurrent setting. The large phase III trial conducted by the European Organisation for the Research and Treatment of Cancer (EORTC) and the National Cancer Institute of Canada (NCIC) demonstrated a significant survival benefit for patients with newly diagnosed glioblastoma who were treated with temozolomide during XRT (ie, concurrent chemoradiation) and as adjuvant therapy thereafter.[6] Statistically significant improvements were noted in progression-free survival (PFS) (median 6.9 vs 5.0 months; $P < .001$), overall survival (median 14.6 vs 12.1 months; $P < .001$), and the 2-year survival rate (26% vs 10%) compared with XRT alone. Moreover, chemoradiation was well tolerated in that study with an excellent safety profile. On the basis of that landmark study reported by Stupp et al.,[6] XRT with concurrent and adjuvant temozolomide has become the standard of care for patients with newly diagnosed glioblastoma.

In addition, a correlative study determined the methylation status of the O^6-methylguanine-DNA methyltransferase (MGMT) promoter region in tumor tissue from patients enrolled in the EORTC/NCIC study. Hypermethylation of the MGMT promoter region silences gene expression with a resultant decrease in MGMT protein synthesis. The correlative study reported by Hegi et al.[7] suggested that MGMT methylation in the tumor was associated with improved survival compared with an unmethylated MGMT promoter (18 vs 12 months, respectively). This observation has generated considerable interest in developing strategies to modulate MGMT activity and thereby improve response and survival. The study by Tolcher et al.[8] demonstrated that dose-dense temozolomide regimens can modulate MGMT activity in the peripheral blood mononuclear cells of treated patients. Tolcher et al. investigated 2 dosing regimens, the 7/14-day schedule (7 consecutive days on treatment followed by 7 days off treatment) and the 21/28-day schedule (21 consecutive days on treatment followed by 7 days off treatment), and showed that there was progressive depletion of MGMT activity throughout the dosing period.[8] Subsequently, Wick et al.[9] reported that the 7/14-day temozolomide regimen yielded a 6-month PFS rate of 48% in patients with recurrent glioblastoma who had not had prior treatment with temozolomide.

In addition to altering the dosing schedule of temozolomide, there has been interest in examining the utility of combining temozolomide with various cytostatic agents that have nonoverlapping toxicity profiles. Several combinations of temozolomide and cytostatic drugs such as thalidomide, isotretinoin, and marimastat have been evaluated in patients with recurrent malignant gliomas, and the preliminary results are promising. Reported 6-month PFS rates were 24% for temozolomide plus thalidomide,[10] 35% for temozolomide plus isotretinoin,[11] and 39% for temozolomide plus marimastat.[12] Preclinical studies using malignant glioma cell lines have also shown that celecoxib exerts both cytostatic and potentially cytotoxic effects in vitro,[13,14] and a study using a C6 rat glioma orthotopic model suggested synergy between temozolomide and celecoxib.[15] These studies support the feasibility and possible utility of combining temozolomide with these agents in the treatment of malignant gliomas, although definite conclusions about the most effective combination cannot be made in the absence of randomized trials.

Therefore, we designed a clinical trial to evaluate the potential benefit of combining a dose-dense adjuvant temozolomide regimen (7/14-day schedule following chemoradiation) with cytostatic agents including thalidomide, isotretinoin, and/or celecoxib. In order to efficiently test all the possible combinations, a randomized factorial design protocol was developed (Fig. 1). This novel design requires accrual of only 22 patients per arm to statistically evaluate the potential benefit of each combination and determine whether there is a benefit to triplet or quadruplet combinations compared with doublet combinations. Although the safety profile of temozolomide in combination with each of these agents individually has been previously established, the safety of the triplet and quadruplet combinations had to be determined in a phase I study before the full phase II protocol could be initiated. The ultimate goal of this study is to develop new treatment regimens that build on the established efficacy of chemoradiation with XRT plus temozolomide for patients with newly diagnosed glioblastoma.

Patients and Methods

Patients

Eligible patients were at least 10 years of age and must have had histologically confirmed supratentorial glioblastoma, a Karnofsky performance status (KPS) greater than 60, adequate bone marrow function (absolute neutrophil count of more than 1500/mm^3 and platelet count greater than or equal to 100 000/mm^3), adequate liver function (serum glutamic pyruvic transaminase and alkaline phosphatase less than 2 times the upper limit of institutional normal [ULN] and bilirubin less than 1.5 times ULN), and adequate renal function (blood urea nitrogen

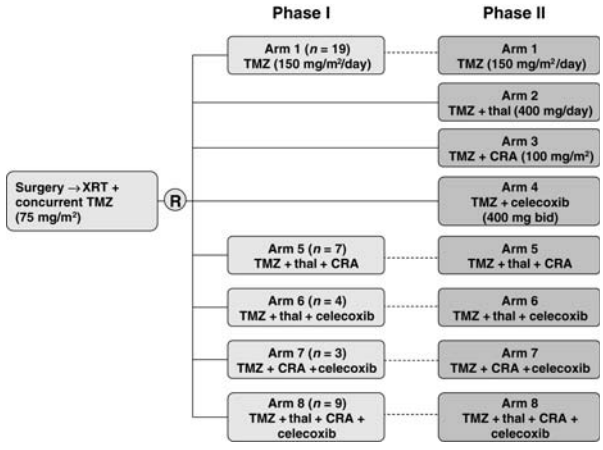

Fig. 1. Phase II factorial study design. XRT, external beam radiation therapy; TMZ, temozolomide; thal, thalidomide; CRA, isotretinoin.

and creatinine less than 1.5 times ULN) within 14 days before enrollment. A baseline postoperative gadolinium-enhanced magnetic resonance imaging (GD-DPTA MRI) scan was performed within 21 days before enrollment. Patients with a history of any other cancer (except nonmelanoma skin cancer or carcinoma in situ of the cervix) were not eligible unless they were in complete remission and off all therapy for that disease for a minimum of 3 years. Patients with serious intercurrent medical illness were excluded. Patients with allergy to sulfa drugs were excluded due to the potential for cross-reactions to celecoxib. Pregnancy was not permitted, and patients of childbearing potential were required to use adequate contraception. All patients were required to provide informed consent, indicating that they were aware of the investigational nature of this study in keeping with the policies of the MD Anderson Cancer Center Institutional Review Board.

Study Design

This phase I/II factorial design study had 8 treatment arms (Fig. 1): arm 1 consisted of single-agent temozolomide; arms 2, 3, and 4 combined temozolomide with 1 other agent (either thalidomide, isotretinoin, or celecoxib); arms 5, 6, and 7 combined temozolomide with 2 agents (either thalidomide + isotretinoin, thalidomide + celecoxib, or isotretinoin + celecoxib); and once the maximum-tolerated doses were determined for these 3 triplet regimens, the quadruplet regimen of temozolomide plus thalidomide, isotretinoin, and celecoxib was tested in arm 8. Patients with evidence of tumor progression 4 weeks after completing chemoradiation were removed from the study before randomization, and new patients were accrued to replace them to evaluate treatment-related toxicity. However, these patients were included in the efficacy analysis. In the phase I portion of the study, treatment with single-agent temozolomide (arm 1) was included to obtain further information on the safety profile of this dose-dense regimen, and no patients were enrolled in arms 2, 3, or 4 because the safety profile of these combinations has been previously established.

The primary endpoint was safety and tolerability. Secondary endpoints were overall median survival and 2-year survival rate.

Treatments

After maximal surgical resection, patients were treated with XRT administered over a period of 6 weeks to a total dose of 60 Gy (2-Gy fractions), and temozolomide (75 mg/m^2/day) was administered daily (7 days per week) for the entire 6 weeks of XRT. Four weeks after completing concurrent chemoradiation, a GD-DPTA MRI scan of the brain was performed, and if there was no evidence of tumor progression, patients were randomized to adjuvant chemotherapy. All patients received adjuvant temozolomide at a dose of 150 mg/m^2/day on the 7/14-day schedule. Patients were treated for a maximum of 12 cycles; each cycle was defined as 28 days.

The starting dose of each agent was determined based on previously published studies.[16–18] The dosing schedules started at the target dose and no dose escalation was performed since the objective was to determine the safety and tolerability of the different combinations. A minimum of 3 patients were enrolled into each treatment arm and if the starting dose was not associated with serious dose-limiting toxicity, that dose was used for the phase II portion of the study and the phase I arm was closed. In the event of any serious dose-limiting toxicity, dose adjustments were allowed for all agents, and additional patients were enrolled in that arm. If 1 of 3 patients developed a serious dose-limiting toxicity, an additional 3 patients were enrolled. If 2 or 3 patients developed a dose-limiting toxicity, an additional 3 patients would be enrolled at the next lower dose level. The phase II dose was defined as the dose level where less than 33% of the patients developed a treatment-related dose-limiting toxicity. Information on the starting dose of each agent and protocol-defined dose adjustments are provided in Table 1.

Assessments

Complete blood count with differential, total protein, albumin, calcium, phosphorus, glucose, blood urea

Table 1. Starting dose and dose adjustments

Treatment arm	Agent	Schedule	Starting dose/day	Dose level		
				−1	−2	−3
1	Temozolomide	Days 1–7, 15–21	*150 mg/m^2	125	100	100
5	Isotretinoin	Days 1–21	*100 mg/m^2	80	60	60
	Thalidomide	Daily	*400 mg	400	400	200
6	Thalidomide	Daily	*400 mg	400	400	200
	Celecoxib	Given twice daily	*800 mg	800	800	400
7	Isotretinoin	Days 1–21	*100 mg/m^2	80	60	60
	Celecoxib	Given twice daily	*800 mg	400	200	200
8	Isotretinoin	Days 1–21	100 mg/m^2	*80	60	60
	Thalidomide	Daily	*400 mg	400	400	200
	Celecoxib	Given twice daily	*800 mg	400	200	200

*Final phase II dose.

nitrogen, creatinine, uric acid, total bilirubin, alkaline phosphatase, lactate dehydrogenase, serum glutamic pyruvic transaminase, serum glutamic oxaloacetic transaminase, and anticonvulsant levels (where appropriate) were performed before randomization and before each cycle of therapy. For patients receiving celecoxib, stools were evaluated for occult blood and creatinine clearance before treatment and every 2 cycles thereafter. For patients receiving isotretinoin, serum cholesterol and triglycerides were assessed before treatment and every 2 cycles thereafter. Among patients receiving thalidomide, prothrombin time and International Normalized Ratio were determined before each cycle of treatment.

Toxicity was assessed at the end of the first 4 weeks of adjuvant treatment (defined as cycle 1) and graded according to the National Cancer Institute's Common Toxicity Criteria (CTC) version 3.0. If dose-limiting adverse events were reported, the dose of the drug was reduced by 1 dose level (to level −1) as indicated in Table 1. Dose-limiting adverse events were defined as any CTC grade 3 or higher nonhematologic toxicity, any CTC grade 3 hematologic toxicity that did not resolve to less than grade 2 within 2 weeks, or any CTC grade 4 hematologic toxicity. If subsequent dose-limiting adverse events occurred at the reduced dose, the dose was reduced to level −2 and finally to level −3. Intolerance to the drugs at level −3 resulted in the patient coming off the study.

Evaluation of treatment effect was performed after every 2 cycles and determined by serial brain-imaging studies, most commonly with GD-DPTA MRI. Radiologic response and progression were evaluated using Macdonald criteria.[19]

Statistical Analysis

Median survival was estimated using the Kaplan–Meier method from time of registration in the trial to time of progression, death, or date of last follow-up. Statistical analysis was done using the SPSS statistical software (version 17.0, 2009, SPSS, Inc.). Toxicity and survival analyses included all patients enrolled in the study.

Results

Patients

A total of 54 patients were accrued to the 5 treatment arms included in the phase I portion of the study (arms 1, 5, 6, 7, and 8). Median age was 52 years, median KPS was 90, and median follow-up was 15.3 months. Baseline patient characteristics are shown in Table 2.

Of the 54 patients accrued, 12 (22%) patients did not receive any adjuvant treatment after chemoradiation, primarily because of evidence of disease progression ($n = 10$) on the GD-DPTA MRI scan performed 4 weeks after XRT. In addition, 1 patient had a severe fungal infection and 1 patient withdrew consent. The remaining 42 patients were randomized to adjuvant therapy with temozolomide monotherapy (arm 1; $n = 19$) or to arm 5 ($n = 7$), arm 6 ($n = 4$), arm 7 ($n = 3$), or arm 8 ($n = 9$). Ten patients discontinued adjuvant treatment because of toxicity, including unresolved neutropenia ($n = 7$), tremors ($n = 1$), fatigue ($n = 1$), and rash ($n = 1$), and 22 patients discontinued treatment before completing all 12 cycles because of disease progression. Dose adjustments were required for 1 patient each in treatment arms 5 and 8 because of dose-limiting toxicity. The final dosing schedule for each arm is indicated in Table 1 by the asterisk (*).

Table 2. Baseline patient and disease characteristics ($n = 54$)

Characteristic	
Median age (range), years	52 (18–76)
Gender, *n* (%)	
Male	32 (59)
Female	22 (44)
Karnofsky performance status, *n* (%)	
100	16 (30)
90	20 (37)
80	14 (26)
70	3 (5)
60	1 (2)

Safety

The most commonly reported adverse events were related to hematologic toxicity. Lymphopenia, as expected, was common and occurred in 63% of patients, with an average duration of 26 days. Neutropenia was noted in 25% of patients, with an average duration of 8 days, although no significant infectious complications were seen during the adjuvant chemotherapy phase of the study. Additionally, thrombocytopenia occurred in 5 (9%) patients. Fatigue was the most frequently reported nonhematologic adverse event, and 10 (18%) patients reported CTC grade 3 fatigue. Seven patients developed thrombotic complications, 4 of whom were randomized to treatment regimens that contained thalidomide. Dose-limiting toxicity occurred in 2 patients during the first cycle of adjuvant treatment. One patient in arm 5 receiving temozolomide plus thalidomide and isotretinoin experienced CTC grade 3 fatigue and rash, and 1 patient in arm 8 receiving all 4 drugs experienced grade 4 neutropenia. Grade 3/4 adverse events by treatment arm are shown in Table 3.

Survival Results

All enrolled patients were included in the survival analysis, including those who did not receive the adjuvant component of treatment because of progression after chemoradiation. As shown in the Kaplan–Meier plot in Fig. 2, the overall median survival was 20 months (95% confidence interval 16.5–23.5 months) and the 2-year survival rate was 40%. The overall median follow-up at the time of this analysis was over 5 years. Ten patients remain alive ranging in length from 4.8 to 6.9 years from entry onto the study.

Table 3. Grade 3/4 adverse events by treatment arm

Adverse event	Patients, grade 3/4						
	Chemoradiation only	Arm 1 ($n = 19$)	Arm 5 ($n = 7$)	Arm 6 ($n = 4$)	Arm 7 ($n = 3$)	Arm 8 ($n = 9$)	Total (adjuvant) ($n = 42$)
Lymphopenia	2/0	14/0	1/4	1/2	0/1	7/1	23/8
Leukopenia	0/0	5/0	4/0	1/0	1/1	5/0	16/1
Thrombocytopenia	1/0	1/0	1/0	0/0	0/1	1/0	4/1
Neutropenia	0/0	3/0	3/1	1/0	1/1	1/3	9/4
Fatigue	3/0	1/0	2/0	2/0	0/0	2/0	10/0
Discontinuations because of adverse events		1	4	3	2	0	10 (24)

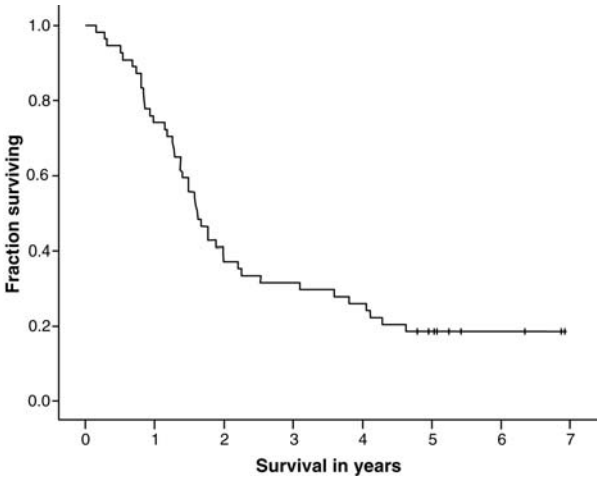

Fig. 2. Kaplan–Meier estimate of survival for all enrolled patients ($n = 54$).

Discussion

Treatment of glioblastoma remains a challenge. Although combined chemoradiation with temozolomide plus XRT followed by adjuvant temozolomide significantly improves survival compared with XRT alone,[6] the majority of patients will eventually fail this treatment, and survival at 2 years remains disappointingly low. A growing body of evidence suggests that increasing the dose intensity of temozolomide may improve time to progression and eventually survival by modulating resistance mechanisms in the tumor.[20] Preliminary data from the subgroup analysis of patients enrolled in the EORTC/NCIC trial support the concept that MGMT plays a significant role in resistance to temozolomide.[7]

The present study evaluated the tolerability of the 7/14-day dose-dense temozolomide schedule in the adjuvant setting following chemoradiation. As previously described by Wick et al.[9] in patients with recurrent glioblastoma, we demonstrated that this regimen is feasible and generally well tolerated. As expected, the most important toxicity was hematologic. As previously described,[21] lymphopenia developed in more than half of the patients. However, no significant risk of infections was observed, despite the fact that patients in the present study did not routinely receive prophylaxis for opportunistic infections. This stands in contrast to other studies with dose-dense temozolomide schedules that have reported a higher incidence of opportunistic infections.[21,22] The combination of cytostatic agents with dose-dense temozolomide resulted in additional toxicity. Of particular importance, these combination regimens may moderately increase the incidence of hematologic toxicity, particularly neutropenia, although there were no apparent infectious complications. The rate of myelotoxicity mandating treatment cessation in this study was 16%, which is higher than the toxicity-related treatment discontinuation rate (9%) reported by Stupp et al. with the conventional single-agent temozolomide at 150–200 mg/m^2 administered on days 1–5 of a 28-day cycle.[6] One interesting observation is the apparent increase in thrombotic events in patients receiving thalidomide. A risk of thrombotic events associated with antiangiogenic agents, including thalidomide, bevacizumab, and sunitinib, has been previously described but the underlying mechanisms remain poorly understood.[23]

Although the phase I portion of this study was primarily designed to determine the safety of dose-dense temozolomide in combination with multiple cytostatic agents, efficacy data were also collected. Although patients with disease progression after completing concurrent chemoradiation were not continued on this study, these patients were included in the efficacy analysis. Therefore, these data closely emulate most published clinical trials in patients with newly diagnosed glioblastoma. With a median follow-up of over 5 years, the observed median survival of 20 months and a 2-year survival rate of 40% compares very favorably with the 14.6-month median survival and 26% 2-year survival rate observed in the chemoradiation arm in the EORTC/NCIC trial reported by Stupp et al.[6] Although these efficacy results look promising, this component of the trial was not powered to truly evaluate efficacy.

In conclusion, the phase I portion of this study demonstrated that a dose-dense schedule of temozolomide is tolerable in the adjuvant setting, and it is feasible to combine it concurrently with as many as 3 cytostatic agents. Preliminary efficacy data suggest that there may be a potential benefit to this approach, although the number of patients receiving any particular combination was small. Successful completion of this phase I study has permitted launching of the full 8-arm phase II

factorial design study as outlined in Fig. 1. We hope to demonstrate the utility and efficiency of the factorial design, which will permit rapid testing of multiple combination regimens in future trials. This is important in light of the rapid development of numerous cytostatic agents with potential activity in gliomas, particularly those designated as signal transduction modulators, and could be further enhanced by incorporation of tumor-based correlative studies.

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Conflict of interest statement. M.R.G. has received honoraria and research support from Genentech and Schering-Plough. V.P. has received an honorarium and travel/accommodation expenses for an educational lecture from Imedex. M.D.G. has received an honorarium and travel/accommodation expenses for educational speaking engagements from Schering-Plough. H.C. acted as a consultant and received an honorarium and travel/accommodation expenses from Schering-Plough in relation to a 2009 advisory board meeting. W.K.A.Y. has acted as a consultant for, and has received honoraria and travel/accommodation expenses from, Merck, Genentech, and Exelixis, and his institution has received a research grant from Novartis. J.Go., K.Hu., K.He., P.G., E.C., C.C., S.W., A.M., J.Gr., V.L. have no relevant conflicts of interest to disclose in relation to this manuscript.

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