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Gemcitabine Plus Radiation Therapy for High Grade Glioma: Long-term Results of a Phase I Dose-Escalation Study

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Abstract

Purpose/Objective(s)—Advancements are needed in the treatment of malignant glioma (HGG), but the benefit of radiosensitizing chemotherapy in all patient subgroups is unknown. We evaluated the tolerability and efficacy of gemcitabine plus radiation (RT) in this phase I study of patients with newly diagnosed HGG.

Methods/Materials—Between 2004–2012, 29 adults with HGG were enrolled. After any extent of resection, RT (60 Gy over 6 weeks) was given concurrent with escalating doses of weekly gemcitabine. Using a time-to-event continual reassessment method (TITE-CRM), 5 dose levels were evaluated starting at 500 mg/m² during the last 2 weeks of RT and advanced stepwise into earlier weeks. The primary objective was to determine the recommended Phase II dose of

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gemcitabine plus RT. Secondary objectives included progression-free survival (PFS), overall survival (OS) and long-term toxicity.

Results—Median follow-up was 38.1 months (range, 8.9-117.5); 24 patients were evaluable for toxicity. After 2005 when standard practice changed, patients with WHO grade IV tumors were no longer enrolled. Median PFS for 22 patients with grade III tumors was 26.0 months (95%CI 15.6-inestimable) and OS was 48.5 months (95%CI 26.8-inestimable). In 4 IDH mutated, 1p/19q codeleted patients, no failures occurred, with all but 1 alive at time of last follow-up. Seven with IDH mutated, non-codeleted tumors with ATRX loss had intermediate OS of 73.5 months (95%CI 32.8-inestimable). Six non-mutated, non-codeleted patients had a median OS of 26.5 months (95%CI 25.4-inestimable). The recommended Phase II dose of gemcitabine plus RT was 750 mg/m²/week given the last 4 weeks of RT. Dose-reductions were most commonly due to grade 3 neutropenia; no grade 4 or 5 toxicities were seen.

Conclusions—Gemcitabine concurrent with RT is well-tolerated and yields promising outcomes, including in patients with adverse molecular features. It is a candidate for further study, particularly for poor-prognosis patient subgroups with HGG.

INTRODUCTION

Early reports of the effect of cranial irradiation (RT) on the blood-brain-barrier (BBB) demonstrate a gradual disruption of the microvascular endothelium during treatment, with a delayed opening of the BBB that holds therapeutic application in the treatment of primary brain tumors.¹ In malignant gliomas, the most common primary brain tumors, local field RT selectively increases the permeability of the blood-tumor barrier in a time and dose-dependent manner, first increasing permeability 1 week into treatment, plateauing after 3 weeks, and then subsiding 1 month after the end of radiation.² These findings suggest that maximal access to tumor by a chemotherapeutic agent may occur during and towards the end of radiation treatment, and that maximal treatment synergy may be achieved by introducing the agent when the blood-tumor barrier has been breached.

Alkylating chemotherapy has demonstrated activity in the treatment of HGG, but its benefit in all patient subgroups is unknown.³⁻⁴ For poor-prognosis patient subgroups, other radiosensitizing agents under active investigation may improve the therapeutic ratio. Preclinical reports of gemcitabine, a potent radiosensitizer at non-cytotoxic concentrations, demonstrate activity in many solid tumor types, including high-grade glioma.⁵ In a murine glioblastoma (GBM) model, growth reduction can be seen as early as 3 days after initiating treatment, and in combination with radiation, gemcitabine improves survival compared to radiation alone.⁶⁻⁷ Gemcitabine crosses the blood-tumor barrier in GBM, but the few clinical studies utilizing gemcitabine as a potential radiosensitizer in high grade glioma show marginal activity.⁸⁻¹⁰ A potential reason for this may relate to the timing of dose administration during the course of radiation.

The aim of this phase I study was to evaluate the toxicity and preliminary efficacy of escalating doses of weekly radiosensitizing gemcitabine concurrent with standard radiation therapy in newly diagnosed high-grade glioma, starting at the end of RT and advancing into earlier weeks to enable maximal drug access to tumor.

PATIENTS AND METHODS

Eligibility

Between 2004 and 2012, adult patients 18 years and older with pathologically confirmed, newly diagnosed WHO grade III or IV supratentorial glioma were enrolled on this prospective study. Patients with grade IV tumors were no longer enrolled after the results of the EORTC/NCIC study established RT and temozolomide as the new standard of care in these tumors.¹¹ Requirements included adequate renal (Cr <1.5 mg/dL), liver (serum bilirubin <2.0 mg/dL and ALT, AST, alkaline phosphatase $2.5 \times$ upper limit of normal), and bone marrow function (total granulocytes $1500/\text{mm}^3$, platelets $100,000/\text{mm}^3$), Karnofsky Performance Status (KPS) ≥ 60 and life expectancy >12 weeks, and no prior brain RT. Patients with CSF dissemination, discontinuous ventricular or meningeal involvement, prior head and neck RT with significant overlap of fields, pregnancy, serious intercurrent illness requiring treatment, or those receiving antineoplastic systemic therapy within 4 weeks prior to start of treatment were excluded. All patients signed study-specific informed consent, and this study was approved by the institutional review board.

Study procedures

Gemcitabine—Five dose levels of gemcitabine were tested, starting in the last 2 weeks of RT when the blood-tumor barrier would most easily be breached and acute toxicity would likely not interfere with the delivery of RT, and advanced stepwise into earlier weeks. The first 2 patients were treated with $500 \text{ mg}/\text{m}^2/\text{week}$ for the last 2 weeks of RT and followed for a full 90 day observation period. Subsequent dose levels were $1000 \text{ mg}/\text{m}^2/\text{week}$ for the last 2 weeks, $1000 \text{ mg}/\text{m}^2/\text{week}$ for the last 3 weeks, $750 \text{ mg}/\text{m}^2/\text{week}$ for the last 4 weeks, and $1000 \text{ mg}/\text{m}^2/\text{week}$ for the last 4 weeks. Level four ($750 \text{ mg}/\text{m}^2/\text{week}$) was added as an intermediate investigational dose to allow increasing weeks of drug delivered without reduction in the total dose. Gemcitabine was administered by a 30-minute IV infusion at the beginning of the week at least 4 hours prior to RT.

Radiation treatment planning—All patients were treated with standard local field RT to 60 Gy in 30 fractions. Gross tumor volume (GTV) was defined as surgical cavity plus any residual enhancing tumor on T1 post-gadolinium MRI. Clinical target volume (CTV1) was defined as GTV + 1.5 cm, and a second, smaller clinical target volume (CTV2) was defined as GTV + 0.5 cm. A 0.5 cm margin was used to create planning target volumes (PTV1 and PTV2, respectively). PTV1 was treated to 46 Gy in 2 Gy fractions, and PTV2 was sequentially boosted for an additional 14 Gy in 2 Gy fractions. Standard immobilization and CT-based planning with MRI fusion was used, and both 3D conformal and IMRT techniques were allowed.

Pathologic and molecular assessment—Patients with evaluable tumor tissue underwent a post-hoc, centralized assessment of prognostic tumor markers, which was correlated with survival outcomes in an exploratory analysis. ATRX (α -thalassemia/mental retardation syndrome X-linked) and IDH status were evaluated by immunohistochemistry, and cases negative for IDH mutation confirmed by PCR and direct sequencing. Immunohistochemistry was performed on 5- μm thick formalin-fixed, paraffin-embedded

tissue sections using antibodies against IDH1-R132H (HO9, 1:200, Dako, Dianova, Hamburg, Germany) and ATRX (HPA001906, 1:1000 Sigma/Atlas, St. Louis, MO).¹²⁻¹³ FISH analysis for 1p and 19q was performed following standard protocols.¹⁴

Objectives and Toxicity Assessment

The primary objective was to determine the maximum tolerated dose (MTD) associated with acute dose-limiting toxicity (DLT) in no more than 20% of patients within 90 days from the start of RT. DLT was defined using National Cancer Institute Common Toxicity Criteria (CTCAE) as any grade 4 or worse neutropenia or thrombocytopenia, any non-reversible grade 3 or worse non-hematologic toxicity related to gemcitabine or RT, any grade 3 hematologic toxicity not improving to grade 2 within 90 days of the start of treatment, any toxicity causing RT to be held for more than 2 weeks not due to tumor progression, or patient death. Weekly doses were held for grade 3-4 hematologic and non-hematologic toxicities, and dose reduced by 50% for subsequent cycles when toxicity had improved to at least grade 2.

Secondary objectives included progression-free (PFS) and overall survival (OS), as well as longer-term toxicity and cognitive outcome as measured by the Folstein mini-mental status examination (MMSE). Patients were evaluated at baseline, weekly during radiotherapy, and every 1-3 months after treatment with neurologic exam including Karnofsky performance status, MMSE and magnetic resonance imaging.

Dose Assignment and Statistical Design

A Time-to-Event Continual Reassessment Method (TITE-CRM) was used to assign patients to gemcitabine dose level.¹⁵⁻¹⁶ Each time a new patient enrolled in the trial, the current probability of toxicity at each dose level was estimated and the newly enrolled patient was assigned to the dose level with estimated probability of toxicity closest to the target rate of 0.20 subject to two safety constraints. First, the assigned dose level could not increase more than 1 level between consecutive patients. Second, a patient could not be assigned to a level unless at least one patient had completed the 90-day acute toxicity observation period at the next lower level. During the trial, the dose-toxicity relationship was modeled via a one parameter logistic regression model. A Bayesian approach was used to estimate posterior mean toxicity probabilities. The trial was originally designed to enroll 36 evaluable patients. Because of accrual rate, the sample size was subsequently reduced to 23 to establish the feasibility and toxicity of treatment.

Due to dose reductions beyond dose level 2 which did not meet the definition of a DLT, the protocol was amended to reduce the weekly dose from 1000 mg/m² to 750 mg/m². This change affected the last 6 patients. A standard 2-parameter logistic regression model was fit with maximum likelihood and used to calculate estimated rates of DLT with associated 90% confidence intervals at each of the 5 dose levels. The Kaplan-Meier method was used to summarize overall survival and progression free survival, and subgroups compared using log-rank statistic.

RESULTS

Patient and treatment characteristics

Twenty-nine patients were enrolled, with 24 evaluable for toxicity. Of 5 inevaluable patients, 2 with GBM had disease progression or died before 90 days due to unrelated respiratory failure from aspiration pneumonia, 1 with grade III glioma had unacceptable treatment delay and 2 with grade III glioma voluntarily withdrew from the study.

Among evaluable patients, the median age was 48 years (range, 23-72), and 14 (58%) were male. Twenty-two patients (92%) had WHO grade III tumors. Among 17 patients with evaluable tissue, 11 (65%) had IDH1 mutation and 4 (25%) with oligodendroglial morphology had 1p/19q co-deletion. Fifteen patients (63%) underwent resection (7 gross total, 8 subtotal); 9 patients underwent biopsy alone (Table 1). All patients were treated with adjuvant temozolomide 150-200 mg/m² beginning approximately 1 month after chemoradiation for a median of 12 cycles (range, 2-24), days 1-5 of a 28-day cycle.

Toxicity and maximum tolerated dose

The maximum tolerated dose of gemcitabine concurrent with standard dose radiation was 750 mg/m²/week given the last 4 weeks of RT. The estimated P(DLT) at this dose level was 0.23 (90% CI 0.10-0.45). DLT events occurred in 4 patients (grade 3 nausea at dose level 3, grade 3 syncope at dose level 4, and grade 3 venous thromboembolism and grade 3 fatigue at dose level 5). After the first 2 dose levels, per protocol dose-reduction occurred in 10 patients, and was due to grade 3 leukopenia and neutropenia in 90% of patients, and grade 3 thrombocytopenia in 1 patient (Table 2). At the recommended Phase II dose, 3 patients had dose-reductions due to grade 3 leukopenia or neutropenia. Chemotherapy was held at week 6 (4th dose) in 2 patients. Chemotherapy was held at week 5 (3rd dose) in one patient, with a 50% dose-reduction for the final week. No patient required transfusions, and no episodes of febrile neutropenia occurred. One patient experienced grade 3 transaminitis that resolved. No grade 4 hematologic or non-hematologic toxicities, and no grade 5 toxicities related to therapy were observed.

All patients completed the full course of RT without treatment break. Two patients developed biopsy-confirmed radiation necrosis without evidence of viable tumor (1 at dose level 1 occurring 11 months after the end of RT, and 1 at dose level 5 occurring 12 months after the end of RT). The latter case was symptomatic including lethargy, headaches and word finding difficulty that responded well to bevacizumab.

Progression-free and overall survival

Median follow-up was 38.1 months (range, 8.9–117.5). For 22 evaluable patients with grade III tumors, median PFS was 26.0 months (95% CI 15.6-inestimable) (14 events), and median OS was 48.5 months (95% CI 26.8-inestimable) (13 deaths). (Figure 1A-B)

Molecular tumor characteristics and survival outcomes

IDH and 1p/19q—Seventeen (77%) patients with grade III tumors had tissue evaluable for IDH mutation status. IDH mutation status was prognostically significant in this cohort.

Median PFS was 49.6 months (95% CI 26.0-inestimable) in 11 patients with IDH1 mutation (6 events), and 11.6 months (95% CI 7.3-inestimable) in 6 patients with IDH wild-type tumors (log-rank $p=0.002$) (6 events). Median OS was also significantly longer in patients with IDH mutation at 73.5 months (95% CI 48.5-inestimable) (4 deaths) versus 26.5 months (95% CI 25.4-inestimable) (6 deaths) (log-rank $p=0.033$).

Sixteen (73%) patients had tissue evaluable for 1p/19q status. Four patients had 1p/19q codeleted tumors, and all were also IDH1 mutated with intact ATRX. At last follow-up, none of the 4 patients experienced disease progression. Median PFS was 26.8 months (95% CI 7.6-inestimable) among 12 patients with non-codeleted tumors (log-rank $p=0.049$) (9 events). Median OS was not reached in the favorable codeleted subgroup compared with 73.5 months in the non-codeleted patients ($p=0.370$) (7 deaths).

Further stratification by IDH mutation and ATRX status demonstrated better outcomes among 5 patients with mutated, non-codeleted tumors with ATRX loss, with a median PFS of 49.6 months (95% CI 26.0-inestimable). Six patients with non-mutated, non-codeleted tumors and intact ATRX had the worst outcome, with median PFS of 11.6 months (95% CI 7.3-inestimable) (log-rank $p=0.007$). Overall survival outcomes paralleled PFS. Median OS among patients with mutated, non-codeleted tumors with ATRX loss was 73.5 months (95% CI 32.8-inestimable), and 26.5 months (95% CI 25.4-inestimable) among patients negative for both with intact ATRX (log-rank $p=0.013$).

Cognitive and functional outcome

Nineteen (90%) of 21 patients with available data had stable or improved MMSE at week 6 of treatment, and 13 (76%) of 17 had stable or improved MMSE 6 months after treatment. Fifteen (94%) of 16 patients had stable or improved performance status 6 months after treatment.

With long-term follow-up, among patients who did not progress, there were no instances of encephalopathy except in 1 patient who also had low levels of B12. All patients except one exhibited good control of seizure activity. Ten to 12 months after treatment, formal MMSE outcomes were only available in 6 patients who did not progress; 5 of 6 patients exhibited stable to improved cognitive function.

DISCUSSION

In this study, we evaluated gemcitabine as a radiosensitizing agent delivered during maximal blood-tumor barrier disruption by local field radiation in patients with newly diagnosed high-grade glioma. The maximum tolerated dose of concurrent weekly gemcitabine was 750 mg/m² over the last 4 weeks of treatment. At this dose level, the highest cumulative dose of gemcitabine was delivered, and no patients required treatment breaks. The most common acute side effect was reversible hematologic toxicity, and with long-term follow-up, only 2 cases of late radiation necrosis (one of which was symptomatic) were observed.

Gemcitabine is a known, potent radiosensitizer with demonstrated activity in a variety of solid tumor malignancies, including bladder and pancreatic cancer.¹⁷⁻¹⁹ Its metabolites

inhibit DNA synthesis and effect radiosensitization by ribonucleotide reductase inhibition as well as redistribution of cells into the early S-phase of the cell cycle, and gemcitabine's effects within the central nervous system are expected to be preferentially selective for proliferating tumor cells over non-proliferating neurons and slowly proliferating glial cells.⁵

Gemcitabine and its radiosensitizing metabolite have been demonstrated to cross the blood-tumor-barrier, a necessary hallmark of any active agent within the central nervous system. The time- and dose-dependent opening of the BBB by radiation may permit increased drug access, as demonstrated by serial imaging studies in which maximal contrast leakage indicative of blood-brain-barrier breakdown is demonstrated 1 week into treatment, plateaus after 3 weeks and persists up to 1 month following therapy. The timing of drug administration in relation to local field radiation, therefore, is expected to influence drug access to tumor, and represents a window of time in which maximal drug concentration may be achieved in synergy with radiation.

This therapeutic window may explain why prior studies utilizing different schedules of gemcitabine in combination with radiation for high-grade glioma demonstrated marginal efficacy. In a prospective study of 21 patients with newly diagnosed glioblastoma in which up to 4 cycles of gemcitabine were delivered prior to initiation of local field radiation alone, median progression-free survival was 8 months, and overall survival 11 months.²⁰ Outcomes were similar in an analogous study delivering neoadjuvant gemcitabine plus treosulfan prior to standard radiation, with a median survival of 12 months.²¹ Reported disease control outcomes were favorable in a phase II study of 23 patients with grade III and IV glioma treated with fixed dose rate gemcitabine at 175 mg/m² weekly for 6 weeks during radiation followed by adjuvant temozolomide, in which disease control was achieved in both methylated (91%) and unmethylated (77.5%) patients. Median PFS and OS outcomes were only 6.8 and 10.1 months, however. Treatment was well-tolerated, with few instances of grade 3 hematologic or hepatic toxicity.¹⁰ Although MGMT status was unavailable for our population, among patients with nonmutated, non-codeleted tumors, which can be expected to behave like glioblastoma, median overall survival achieved was 26.5 months.

Although temozolomide and RT has become the de facto treatment for malignant glioma in the United States due to ease of administration and more favorable toxicity profile, its efficacy compared to the historical standard of combination chemotherapy with PCV is still a matter of ongoing study.²² Outcomes in our study compare favorably with outcomes among patients treated with RT followed by PCV chemotherapy in the EORTC 26951 trial, with median PFS of 26.0 months and median OS of 48.5 months among patients in our study, compared with 24.3 months and 42.3 months among patients treated with RT plus PCV, and 13.2 months and 30.6 months among patients treated with RT alone, respectively.³

The value of alkylating chemotherapy is of greater debate in unfavorable molecular subgroups with intact 1p/19q and wild-type IDH, in whom survival outcomes are worse and in whom the addition of alkylating chemotherapy has not demonstrated an improvement in overall survival. For these patients, an intensification of local therapy with concurrent radiosensitizing gemcitabine may be an effective, well-tolerated treatment option. In our

study, with a median follow-up of 38.1 months, patients with IDH mutant, 1p/19q codeleted molecular oligodendrogial tumors had the best outcome, with no failures observed and all but 1 patient still alive at time of last follow-up. Median survival of the intermediate subgroup with mutated, non-codeleted tumors (most with ATRX loss in our series) was 73.5 months, comparing favorably with outcomes in the exploratory analysis of RTOG 9402, where median survival in the chemoradiation arm was 52.8 months. Outcomes among non-mutated, non-codeleted patients compared favorably with reported survival in patients treated with alkylating chemotherapy and radiation in RTOG 9402, 26.5 months vs 12 months, and with radiation alone.⁴ Evaluated molecular biomarkers including 1p/19q and IDH demonstrated expected prognostic significance in this cohort of patients treated with standard radiation therapy and concurrent gemcitabine.²³ Although patient subgroups were small, a distinct stratification in outcome was observed in our series. Moreover, the reversible, myelosuppressive effects of gemcitabine seen in our study did not lead to any treatment breaks or grade 4 or 5 toxicity. In contrast, 14% and 32% of patients experienced grade 4, principally hematologic toxicity during PCV chemotherapy in the EORTC and RTOG studies, respectively, and two early deaths attributable to PCV-induced neutropenia were reported in the RTOG trial.²⁴⁻²⁶

Given the limited patient numbers in this phase I trial, definitive conclusions about the efficacy of this regimen cannot be drawn. Strengths of this study include the Bayesian design allowing efficient dose-escalation and accrual concentrated around the target dose with preliminary estimates of efficacy, centralized pathologic and molecular assessment, serial evaluation of cognitive function and performance status, as well as long-term follow-up, which provides a first-time, multi-dimensional assessment of this treatment approach, particular in poor-prognosis patient subsets.

In conclusion, radiosensitizing gemcitabine plus radiation is a tolerable regimen with a favorable acute and long-term toxicity profile compared to the historical standard of PCV chemotherapy, as well as preserved long-term cognitive and functional outcomes among patients treated with this regimen. Survival rates among molecular subgroups are promising compared with patients treated with alkylating chemotherapy regimens and should be further evaluated, particularly in poor-prognosis patient subsets as a well-tolerated alternative to alkylating chemotherapy or radiation therapy alone.

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In this phase I study of escalating doses of gemcitabine initially given during the last 2 weeks of radiation and advancing stepwise into earlier weeks for patients with high-grade glioma, the maximum tolerated dose was 750 mg/m²/week during the last 4 weeks of radiation. This regimen was associated with acceptable acute and long-term toxicity, and the favorable survival outcomes reported here support further investigation as a well-tolerated alternative to alkylating chemotherapy or radiation therapy alone.

Figure 1A.
Progression-free survival among patients with grade III glioma (n=22)

Figure 1B.
Overall survival among patients with grade III glioma

Table 1

Baseline patient, tumor and treatment characteristics

Characteristic	Number
Median age (range)	48 (23-72)
Gender Male Female	14 10
KPS <90 90	8 16
Baseline MMSE <27 27	3 21
RPA classification I II III IV	5 3 7 9
Extent of surgery Gross total resection Subtotal resection Biopsy	7 8 9
Histology Anaplastic oligodendroglioma Anaplastic oligoastrocytoma Anaplastic astrocytoma Glioblastoma	5 10 7 2
1p/19q status Codeleted Intact Unknown	4 12 8
IDH1 status* Mutated Wild-type Unknown	11 6 7
ATRX loss Yes No Unknown	5 8 11

* IDH1 R132H in all cases except 1 case of R132C

Table 2

Rates of dose-limiting toxicity, dose-reductions and total dose received per dose-level

Dose level	Assigned Weeks Gem during RT	Assigned Weekly Dose	# DLTs/ # patients	P(DLT)* (90% CI)	Dose reductions	Median total dose received (mg/m ²)
1	5,6	500	0/6	0.01 (0.00-0.26)	0	1000
2	5,6	1000	0/2	0.03 (0.00-0.28)	0	2000
3	4,5,6	1000	1/6	0.09 (0.02-0.32)	3	2500
4	3,4,5,6	750	1/6	0.23 (0.10-0.45)	3	2625**
5	3,4,5,6	1000	2/4	0.48 (0.18-0.79)	4	2500

* Estimated rate of DLT using logistic regression methods

** Imputed total dose to account for a single missed dose by one patient due to insurance reasons, not related to toxicity