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ORIGINAL REPORT

Randomized Phase II Trial of Chemoradiotherapy Followed by Either Dose-Dense or Metronomic Temozolomide for Newly Diagnosed Glioblastoma

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ABSTRACT

Purpose
Alternative dosing schedules of temozolomide may improve survival in patients with newly diagnosed glioblastoma (GBM) by increasing the therapeutic index, overcoming common mechanisms of temozolomide resistance, or both. The goal of this randomized phase II study was to evaluate two different temozolomide regimens in the adjuvant treatment of newly diagnosed GBM.

Patients and Methods
Adult patients with newly diagnosed GBM were randomly assigned to receive standard radiotherapy with concurrent daily temozolomide followed by six adjuvant cycles of either dose-dense (150 mg/m^2 days 1 to 7 and 15 to 21) or metronomic (50 mg/m^2 continuous daily) temozolomide. Maintenance doses of 13-*cis*-retinoic acid were then administered until tumor progression. The primary end point was overall survival (OS) at 1 year. Tumor tissue was assayed to determine O^6-methylguanine–DNA methyltransferase (*MGMT*) promoter methylation status.

Results
Eighty-five eligible patients were enrolled; 42 were randomly assigned to dose-dense and 43 to metronomic temozolomide. The 1-year survival rate was 80% for the dose-dense arm and 69% for the metronomic arm; median OS was 17.1 months (95% CI, 14.0 to 28.1 months) and 15.1 months (95% CI, 12.3 to 18.9 months), respectively. The most common toxicities were myelosuppression (leukopenia, neutropenia, and thrombocytopenia) and elevated liver enzymes. Pseudoprogression was observed in 37% of assessable patients and may have had an impact on estimates of progression-free survival (6.6 months in the dose-dense arm and 5.0 months in the metronomic arm).

Conclusion
Both dose-dense and metronomic temozolomide regimens were well tolerated with modest toxicity. The dose-dense regimen appears promising, with 1-year survival of 80%.

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INTRODUCTION

Despite recent advances, treatment of glioblastoma (GBM) remains a challenge, and newly diagnosed patients have a dismal prognosis. The classic treatment paradigm was aggressive surgical resection followed by involved-field radiation, which resulted in an expected survival of 9 to 12 months. A recent international phase III randomized trial by the EORTC/NCIC (European Organisation for Research and Treatment of Cancer/National Cancer Institute of Canada) comparing radiotherapy (RT) alone with concomitant RT and temozolomide followed by six cycles of adjuvant temozolomide clearly established the benefit of systemic chemotherapy in GBM.[1] The trial showed significant improvement in survival for the combined arm over RT alone and established a new standard of care; however, median survival remained poor at 14.6 months.

Optimizing the adjuvant chemotherapy regimen is one potential strategy for improving patient outcomes. Successful strategies for optimizing the therapeutic index of chemotherapy in other solid tumors have included combinations of chemotherapy, dose intensification, and alternate delivery schedules. Experimental and clinical data demonstrate that temozolomide response is schedule dependent, and alternative dosing regimens may enhance efficacy by several potential mechanisms. In particular, more frequent dosing may improve

inhibition of O^6-alkylguanine–DNA alkyltranferase (enzyme encoded by the methylguanine methyltransferase [*MGMT*] gene), preventing recovery from DNA mutations introduced by alkylating agents such as temozolomide,[2] a major mechanism of resistance in GBM.

In the EORTC/NCIC trial, patients whose tumor had a methylated *MGMT* gene promoter had improved survival relative to those with an unmethylated *MGMT* promoter.[3] Moreover, the benefit of adding temozolomide to RT was less clear in patients with unmethylated *MGMT* promoter. Thus, more effective inhibition of O^6-alkylguanine–DNA alkyltranferase may be most beneficial to patients with unmethylated *MGMT* promoter.

Metronomic or continuous daily dosing with chemotherapy has a direct toxic effect on endothelial cells in tumor vasculature and is postulated to have combined antitumor and antiangiogenic effects.[4-6] Furthermore, continuous exposure to low-dose temozolomide results in more continuous inhibition of O^6-alkylguanine–DNA alkyltransferase and may improve the efficacy of temozolomide, particularly in patients with unmethylated *MGMT*. Clinically, extended schedules of temozolomide have been safe and effective in patients with recurrent malignant glioma.[7-10]

Dose-dense chemotherapy is based on the Norton-Simon model of cell proliferation. This model states that a dose of chemotherapy will have a fixed cell kill rate regardless of tumor size; therefore, decreasing the time interval between doses (increasing dose density) will improve overall efficacy by minimizing the opportunity for tumor cell regrowth between cycles.[11] This concept can be actualized by using growth factor support and blood product transfusion to maintain a dose-dense treatment schedule without interruption. Temozolomide can be delivered at standard doses for 7 days every other week (150 mg/m^2 days 1– to 7 and 15 to 21 of a 28-day cycle) thereby approximating the dose-dense concept. This dose-dense temozolomide regimen is feasible[12] and potentially more efficacious than standard dosing in recurrent GBM.[13] In addition, more frequent dosing will inhibit O^6-alkylguanine–DNA alkyltransferase.

We hypothesized that either the dose-dense or metronomic dosing regimen of adjuvant temozolomide could have increased efficacy relative to standard dosing. Therefore, we designed a randomized phase II trial to evaluate these regimens compared with historical controls and, if appropriate, to recommend one arm for a phase III trial. To facilitate use of the EORTC/NCIC phase III trial as a historical benchmark,[1] patients received six cycles of adjuvant temozolomide. However, given the propensity for GBM to recur, the concept of a maintenance therapy to prolong remission had strong appeal. There is evidence that retinoids induce differentiation in glioma cells,[14] and inhibit both proliferation and invasiveness[15,16]; 13-*cis*-retinoic acid has shown promise as an agent capable of maintaining remission in malignant gliomas.[17] Therefore, 13-*cis*-retinoic acid was incorporated as maintenance therapy for patients without tumor progression after six cycles of adjuvant temozolomide.

PATIENTS AND METHODS

Eligibility

Patients with newly diagnosed, pathologically confirmed GBM were eligible. This single-center, prospective randomized trial enrolled patients from August 2005 through December 2007. The protocol was reviewed and approved by the institutional review board at Memorial Sloan-Kettering Cancer Center (New York, NY); all patients provided written informed consent.

Patients were between 18 and 70 years of age; Karnofsky performance status (KPS) was $\geq$ 60%. Concurrent active malignancy was prohibited, and baseline laboratory function was required as follows: absolute neutrophil count $\geq$ 1,500/μL, platelet count $\geq$ 100,000, AST less than 2.5$\times$ the upper limit of normal (ULN), total bilirubin 2$\times$ ULN, and creatinine 2$\times$ ULN. Pregnant or nursing patients were excluded.

Treatment Plan

All patients received focal external-beam RT using conventional radiation planning to approximately 60 Gy ($\pm$5% total dose), with concurrent temozolomide at 75 mg/m^2 daily throughout the course of RT. Intensity-modulated RT was allowed.

Adjuvant Chemotherapy

Patients were randomly assigned to receive dose-dense or metronomic temozolomide. Both regimens were administered for six cycles of 28 days. The dose-dense arm received temozolomide 150 mg/m^2 daily days 1 to 7 and 15 to 21 of each cycle. The metronomic arm received temozolomide 50 mg/m^2 daily days 1– to 28 of each cycle. Antiemetic and other supportive therapies were delivered at the discretion of the treating physician. Growth factor support was allowed and encouraged to ensure delivery of therapy, particularly on the dose-dense arm. Treatment continued until tumor progression, development of excessive toxicity, withdrawal of consent, or completion of six cycles (Fig 1).

Maintenance Therapy With 13-cis-Retinoic Acid

If a patient completed six cycles of adjuvant temozolomide without evidence of clinical or radiographic progression, therapy was changed to single-agent 13-*cis*-retinoic acid 100 mg/m^2 daily days 1 to 21 of a 28-day cycle. Maintenance therapy was continued until tumor progression, development of excessive toxicity, or withdrawal of consent.

Evaluation During Treatment

Postoperative magnetic resonance imaging (MRI) was used as the initial baseline study. The first repeat MRI scan was obtained 2 to 4 weeks after completion of chemoradiotherapy and served as a new baseline for subsequent MRI comparisons. Follow-up MRIs were performed after every other cycle of temozolomide or 13-*cis*-retinoic acid or approximately every 8 weeks. Response was evaluated via Macdonald criteria[18]; these criteria incorporate corticosteroid dosage and clinical status in addition to imaging findings.

In addition to assessing radiographic response or tumor progression, MRIs were assessed for pseudoprogression.[19,20] The rate of pseudoprogression in this trial was assessed as follows[21]: patients whose first post-RT MRI showed increased gadolinium enhancement relative to their postoperative scan were started on adjuvant temozolomide as per trial protocol. Their next MRI scan was compared with the post-RT scan; if it showed stable or improved enhancement, they were considered to have pseudoprogression and continued on study. If the MRI showed continued increase in enhancement, this was considered tumor progression. If re-resection was performed for a recurrent mass lesion, histologic interpretation formed the basis for definitive diagnosis (treatment-related necrosis *v* recurrent tumor).

National Cancer Institute Common Terminology Criteria of Adverse Events, version 3.0, was used for toxicity evaluation. Available tumor samples were analyzed by Oncomethylome Sciences (Amsterdam, the Netherlands) using methylation-specific polymerase chain reaction to determine *MGMT* methylation status.

Trial Design and Statistics

The primary objective was to evaluate overall survival (OS) at 1 year for each treatment arm. The trial was not powered to compare arms, but rather to compare each arm with a historical control; the temozolomide arm of the EORTC/NCIC trial,[1] which had a 12-month survival rate of 61%, was used as the historical control. For this trial, a 1-year survival of 70% in either arm would be considered promising, and that arm would be recommended for development of future studies.

Patients were stratified by KPS ($\geq$ 80% *v* $<$ 80%) and randomly assigned at time of enrollment via the random permuted block method. A two-stage Simon's minimax design was used: the first 23 patients randomly assigned to each arm were assessed; if at least 12 were alive at 1 year, an additional 16 were to be accrued to that arm. Therefore, the planned sample size, if both stages of

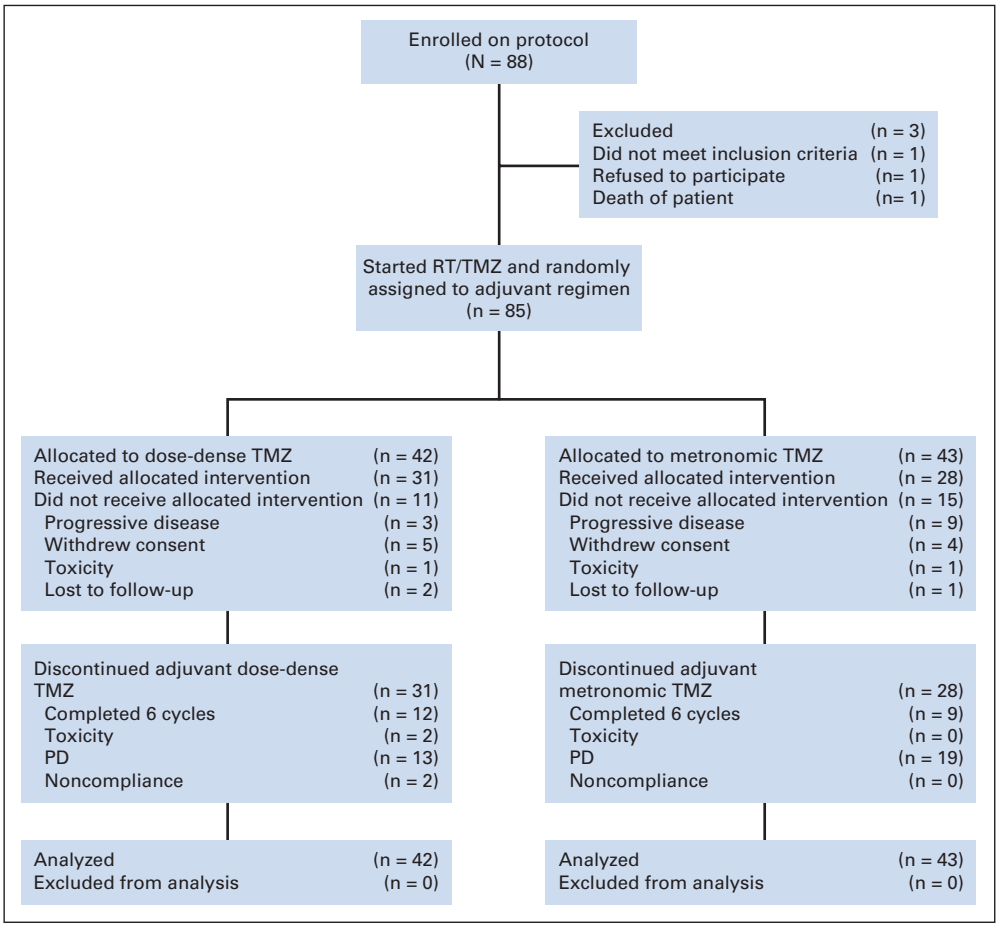

Fig 1. CONSORT diagram. RT, radiotherapy; TMZ, temozolomide; PD, progressive disease.

both arms were fully accrued, was 78 patients. To account for patient attrition, the sample size was overaccrued by 10%, for a total of 85 planned patients. Each arm was powered to provide ≥ 90% probability of obtaining a negative result if the true 1-year OS was 50% and ≥ 90% probability of obtaining a positive result if the true 1-year OS was 70%.

All patients who received at least one dose of initial treatment (concurrent temozolomide and RT) were included in the analysis on an intent-to-treat basis. Progression-free survival (PFS) was defined as the time from study entry to date of disease progression or death; OS was defined as the time from study entry to date of death as a result of any cause. Kaplan-Meier methodology was used to characterize OS and PFS. Potential prognostic factors, including age, sex, KPS, extent of resection, and *MGMT* status were analyzed using the Cox proportional hazards regression model to identify variables that were independently predictive of outcome. Factors with $P \leq .2$ on univariate analyses were entered as candidate variables in the multivariate analysis. Follow-up extends through December 15, 2008.

RESULTS

Patient Characteristics

Eighty-five eligible patients were enrolled and started treatment with temozolomide and RT; 42 were randomly assigned to dose-dense temozolomide and 43 to metronomic temozolomide (Table 1). Median age of the entire cohort was 56.3 years; 65% of patients were males. Median KPS score was 90%; 73% of patients had a KPS score ≥ 80%. Thirty-nine percent of patients underwent gross total resection, 39% subtotal resection, and 22% biopsy only. Tumor tissue was available for *MGMT* assay in 68 patients, 39 had unmethylated *MGMT*, and nine had methylated *MGMT*; in 20 patients, the tissue sample was inadequate for analysis.

Treatment Administration

Fifty-nine patients (69%) began adjuvant treatment as planned, 31 on the dose-dense arm and 28 on the metronomic arm. Reasons for not starting planned adjuvant therapy included disease progression,[12] excess toxicity,[2] voluntary patient withdrawal,[9] and loss to follow-up.[3] The 31 patients on the dose-dense arm completed a median of four cycles of adjuvant temozolomide; the aggregate number of cycles delivered to this cohort was 116. The 28 patients on the metronomic arm received a median of four cycles of adjuvant temozolomide; the aggregate number of cycles delivered to this cohort was 105. Twenty-one patients who completed six cycles of adjuvant temozolomide were eligible to receive maintenance 13-*cis*-retinoic acid therapy; however, only six patients received maintenance 13-*cis*-retinoic acid for two to 11 cycles. Nine patients developed tumor progression shortly after completion of six cycles and were unable to initiate 13-*cis*-retinoic acid therapy; five patients refused to stop temozolomide, and one patient discontinued temozolomide but refused 13-*cis*-retinoic acid therapy.

Toxicity

Both adjuvant regimens were well tolerated, and no unexpected toxicities or rates of toxicity were observed (Table 2). Grade 3 lymphopenia was common but was not associated with clinically significant findings (no *Pneumocystis carinii* pneumonia was observed), and

Table 1. Patient Characteristics

Characteristic	All Patients (N = 85)		Dose-Dense Therapy (n = 42)		Metronomic Therapy (n = 43)	
	No.	%	No.	%	No.	%
Age, years						
Median	56.3		59.1		54.1	
Range	21-71		30-70		21-71	
Sex						
Male	56		29		27	
Female	29		13		16	
Median KPS, %	90		90		90	
Extent of surgery						
GTR	33	39	18	43	15	35
STR	33	39	14	33	19	44
Biopsy	19	22	10	24	9	21
Median time from diagnosis to starting treatment, weeks	4.0		4.0		3.9	

Abbreviations: KPS, Karnofsky performance status; GTR, gross total resection; STR, subtotal resection.

treatment was not modified for lymphopenia. Myelosuppression and fatigue were more frequent among patients on the dose-dense arm; aminotransferase elevations were more frequent on the metronomic arm. No patients developed grade 3 or 4 nausea, vomiting, or constipation at any point during the trial. Two patients were unable to tolerate dose-dense temozolomide because of persistent or recurrent myelosuppression despite growth factor support.

Pseudoprogression

The post-RT MRI showed increased enhancement in 35 patients consistent with possible pseudoprogression. Seventeen were eventually determined to have true progression (13 by MRI, four by histology at re-resection); eight patients changed therapy post-RT and could not be assessed. Overall, 10 patients (37%) were categorized as true pseudoprogression: eight by MRI criteria and two by histology (Fig 2).

Magnetic resonance (MR) perfusion imaging was available in two patients with pseudoprogression and showed elevated relative cerebral blood volume (rCBV). Five patients with true progression had MR perfusion imaging; four had elevated rCBV and one had reduced rCBV. In addition, two patients with pseudoprogression had hypermetabolism on [^{18}F]fluorodeoxyglucose positron emission tomography (PET) scans in the area of increased enhancement; no patients with progression had PET scans.

Response and Survival

OS. Median OS for the entire cohort is 16.4 months (95% CI, 14.9 to 18.0); 39% of patients were alive at last follow-up, and median follow-up for surviving patients was 18.8 months (Fig 3). Twelve-month OS was 74% (95% CI, 65 to 83) for the entire cohort, 80% (95% CI, 67 to 92) for the dose-dense arm, and 69% (95% CI, 55 to 83) for the metronomic arm. Twenty-four–month survival was 34.8% (95% CI, 18 to 52) and 28% (95% CI, 13 to 43), respectively, for the two arms.

Median OS (Table 3) was 17.1 months (95% CI, 14.0 to 28.1) for the dose-dense cohort and 15.1 months (95% CI, 12.3 to 18.9) for the metronomic cohort. When analysis was restricted to the 59 patients who actually received adjuvant chemotherapy as planned, median OS was 17.8 months (95% CI, 14.0 to not reached) for the dose-dense group and 16.3 months (95% CI, 13.3 to 18.9) for the metronomic group; 12-month OS was 84% for the dose-dense group and 79% for the metronomic group.

Median survival in the 39 patients with unmethylated *MGMT* was 14.9 months overall (95% CI, 13.0 to 16.0): 15.4 months (95% CI, 13.0 to not reached) in those receiving dose-dense temozolomide and 13.5 months (95% CI, 10.2 to 15.5) in those receiving metronomic temozolomide. Median OS in the nine patients with methylated *MGMT* was 28.1 months (95% CI, 18.0 to not reached).

Table 2. Grade 3 or 4 Toxicities

Toxicity	Radiotherapy/ Temozolomide (n = 85)		Adjuvant Therapy Type			
			Dose Dense (n = 31)		Metronomic (n = 28)	
	No.	%	No.	%	No.	%
Leukopenia	16	19	6	19	4	14
Neutropenia	11	13	3	10	2	7
Lymphopenia	20	23.5	21	68	17	61
Thrombocytopenia	6	7	1	3	2	7
Elevation of aminotransferases	5	6	1	3	5	18
Fatigue	4	5	3	10	1	4

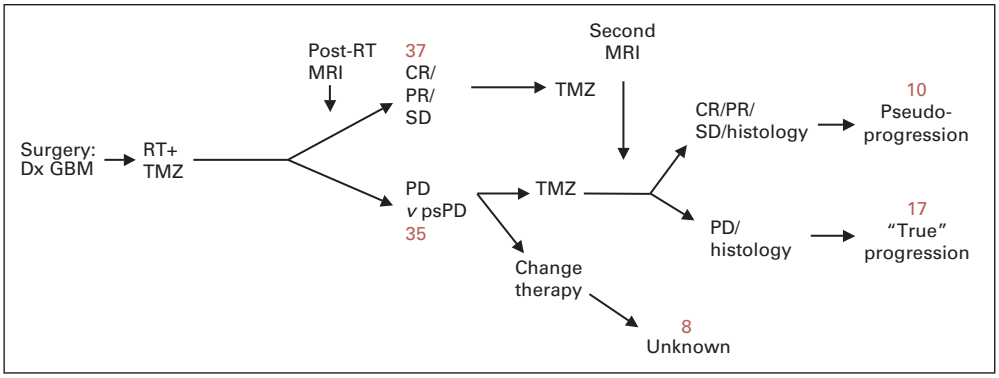

Fig 2. Evaluation for pseudoprogression (psPD). Dx, diagnosis; GBM, glioblastoma; RT, radiotherapy; TMZ, temozolomide; MRI, magnetic resonance imaging; CR, complete response; PR, partial response; SD, stable disease; PD, progression of disease.

PFS. Median PFS for the entire cohort was 6.1 months (95% CI, 4.4 to 7.7); 75% of patients had experienced disease progression at last follow-up. Median PFS was 6.6 months (95% CI, 4.2 to 7.8) for the dose-dense arm and 5.0 months (95% CI, 4 to 6.7) for the metronomic arm. Median PFS in the 39 patients with unmethylated *MGMT* was 5 months (95% CI, 4.0 to 7.9); median PFS in the nine patients with methylated *MGMT* was 4.2 months (95% CI, 3.4 to not reached).

Multivariate Analysis

On univariate analysis, age, sex, KPS, extent of surgery, and *MGMT* methylation were identified as candidate variables for OS. In the multivariate model, only KPS and extent of resection reached independent significance; however, there was a trend toward significance for both age and *MGMT* status (Table 4).

DISCUSSION

Our results demonstrate that it is feasible to deliver increased total doses of temozolomide in the adjuvant setting with modest improvements in survival. The dose-dense arm achieved a 12-month OS rate of 80% on intent-to-treat analysis, which was a predetermined end point of sufficient interest to move forward into a prospective phase III trial. In particular, patients with unmethylated *MGMT* promoter may have derived benefit from dose-dense temozolomide because their median survival was 15.4 months, which is superior to the 12.7 months reported for the patients with unmethylated *MGMT* who received temozolomide on the EORTC/NCIC trial.[3]

A wide range of alternative dosing schedules has been developed and reported for temozolomide administration. The rationale for alternate dosing included increased drug delivery, allowing combinations with other therapies, enhanced therapeutic index, or diminished toxicity. We selected two different temozolomide schedules, each with appropriate scientific and clinical rationale for improving the therapeutic index as well as potentially abrogating underlying mechanisms of temozolomide resistance. This two-arm trial was designed not to compare the regimens directly, but rather to test each regimen against the historical control for adequate signal of efficacy for further development. Although the continuous low daily dosing of metronomic temozolomide was well tolerated, there was no evidence that this schedule was superior to standard dosing.[1] Furthermore, metronomic dosing of temozolomide is significantly more expensive than standard dosing and cannot be recommended.

The dose-dense delivery schedule met the primary end point, suggesting that decreasing the time interval between dosing cycles may be an effective strategy in malignant glioma. At least four other studies have investigated this dose-dense schedule in malignant glioma.[22] The most impressive results reported a 6-month PFS of 48% in patients with recurrent malignant glioma with low rates of associated toxicity.[13] A study of this regimen in newly diagnosed inoperable glioblastoma documented a 25% radiographic response rate although OS was poor.[23] Further development of dose-dense temozolomide might employ more aggressive or mandatory growth factor support and escalation of temozolomide dose in patients with minimal myelosuppression at 150 mg/m^2. However, if the benefit from the

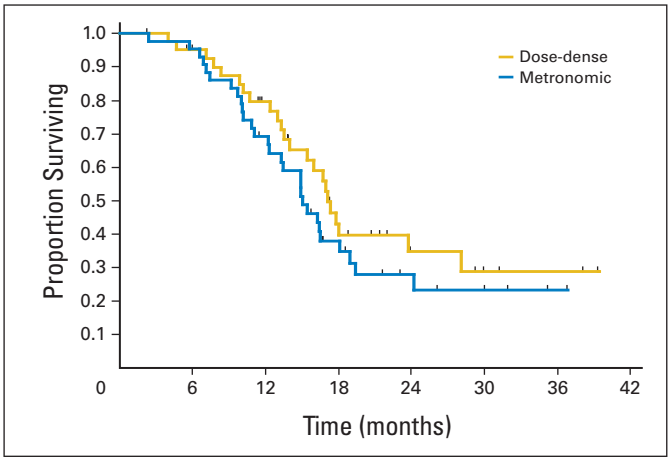

Fig 3. Overall survival by treatment arm.

Table 3. Survival Data

Survival	All Patients (%)	Dose-Dense Therapy (%)	Metronomic Therapy (%)
Overall survival, months			
Median	16.4	17.1	15.1
12 month	74	80	69
24 month	31	35	28
Progression-free survival, months			
Median	6.1	6.6	5.0
6 month	51	56	46

Table 4. Multivariate Analysis of Overall Survival

Variable	Overall Survival		
	P	Hazard Ratio	95% CI
Age	.10	1.04	0.99 to 1.08
Sex, female	.61	0.80	0.35 to 1.85
KPS ≤ 80%	.03	2.35	1.09 to 5.07
Surgery			
Gross total		Reference	—
Subtotal		2.20	0.96 to 5.05
Biopsy	.01	7.40	1.97 to 27.8
Unmethylated *MGMT* promoter	.15	2.38	0.72 to 7.81

Abbreviations: KPS, Karnofsky performance status; *MGMT,* O^6-methylguanine–DNA methyltransferase gene.

dose-dense delivery schedule is largely inhibition of *MGMT* recovery between cycles of therapy, further dose escalation may not be warranted, and combination with other active agents may be more reasonable.

PFS was not a primary end point of this study, and the observed PFS was similar to that reported by the EORTC/NCIC trial. Although this could be interpreted as a negative result of this study, we believe it more appropriately highlights the challenges raised by MRI interpretation, particularly initial radiographic assessment after a combination of chemotherapy and radiotherapy. Pseudoprogression is increasingly recognized as a major limitation on routine imaging, and we adopted a conservative definition of pseudoprogression that may have underestimated the true incidence. However, at this time there is no widely accepted definition, and supplemental imaging with MR perfusion or PET did not reliably distinguish true progression from pseudoprogression in our patients. In contrast to reported correlations of pseudoprogression with outcome and *MGMT* status,[24] we found no evidence that pseudoprogression correlated with survival, and no patient with pseudoprogression in this study had methylated *MGMT*, although our sample size was too small to draw definitive conclusions (data not shown). It is possible that some patients who were removed from our study for progression in fact had pseudoprogression, shortening our estimated PFS. Pseudoprogression will remain an important issue in the design and interpretation of newly diagnosed GBM studies, potentially limiting the utility of PFS for intertrial comparisons in this patient population.

Our study is limited by the relatively small sample size as well as overall receipt of planned adjuvant therapy. More than 10% of patients declined to start adjuvant therapy, and nearly 15% were determined to have progression on their immediate post-RT MRI and were not continued on adjuvant treatment as planned. Finally, a significant hypothesis of the current study was that more intensive drug delivery would benefit patients with unmethylated *MGMT,* and we were able to obtain informative *MGMT* status in only slightly more than half the patients. The EORTC/NCIC trial had similar limitations with acquisition of adequate tumor tissue and stressed the importance of prospective collection of high-quality tumor tissue for standardized assays. Despite these limitations, dose-dense temozolomide warrants further investigation in a randomized controlled trial.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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