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ORIGINAL ARTICLE

Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma

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ABSTRACT

BACKGROUND

Glioblastoma, the most common primary brain tumor in adults, is usually rapidly fatal. The current standard of care for newly diagnosed glioblastoma is surgical resection to the extent feasible, followed by adjuvant radiotherapy. In this trial we compared radiotherapy alone with radiotherapy plus temozolomide, given concomitantly with and after radiotherapy, in terms of efficacy and safety.

METHODS

Patients with newly diagnosed, histologically confirmed glioblastoma were randomly assigned to receive radiotherapy alone (fractionated focal irradiation in daily fractions of 2 Gy given 5 days per week for 6 weeks, for a total of 60 Gy) or radiotherapy plus continuous daily temozolomide (75 mg per square meter of body-surface area per day, 7 days per week from the first to the last day of radiotherapy), followed by six cycles of adjuvant temozolomide (150 to 200 mg per square meter for 5 days during each 28-day cycle). The primary end point was overall survival.

RESULTS

A total of 573 patients from 85 centers underwent randomization. The median age was 56 years, and 84 percent of patients had undergone debulking surgery. At a median follow-up of 28 months, the median survival was 14.6 months with radiotherapy plus temozolomide and 12.1 months with radiotherapy alone. The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). The two-year survival rate was 26.5 percent with radiotherapy plus temozolomide and 10.4 percent with radiotherapy alone. Concomitant treatment with radiotherapy plus temozolomide resulted in grade 3 or 4 hematologic toxic effects in 7 percent of patients.

CONCLUSIONS

The addition of temozolomide to radiotherapy for newly diagnosed glioblastoma resulted in a clinically meaningful and statistically significant survival benefit with minimal additional toxicity.

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Glioblastoma is the most frequent primary malignant brain tumor in adults. Median survival is generally less than one year from the time of diagnosis, and even in the most favorable situations, most patients die within two years.[1-3] Standard therapy consists of surgical resection to the extent that is safely feasible, followed by radiotherapy; in the United States, adjuvant carmustine, a nitrosourea drug, is commonly prescribed.[4,5] Cooperative-group trials have investigated the addition of various chemotherapeutic regimens to radiotherapy,[6-9] but no randomized phase 3 trial of nitrosourea-based adjuvant chemotherapy has demonstrated a significant survival benefit as compared with radiotherapy alone, although there were more long-term survivors in the chemotherapy groups in some studies.[10] A meta-analysis based on 12 randomized trials suggested a small survival benefit of chemotherapy, as compared with radiotherapy alone (a 5 percent increase in survival at two years, from 15 percent to 20 percent).[11] The meta-analysis included 37 percent of patients with prognostically more favorable, lower-grade gliomas.

Temozolomide, an oral alkylating agent, has demonstrated antitumor activity as a single agent in the treatment of recurrent glioma.[12-14] The approved conventional schedule is a daily dose of 150 to 200 mg per square meter of body-surface area for 5 days of every 28-day cycle. Daily therapy at a dose of 75 mg per square meter for up to seven weeks is safe; this level of exposure to temozolomide[15] depletes the DNA-repair enzyme O^6-methylguanine-DNA methyltransferase (MGMT).[16] This effect may be important because low levels of MGMT in tumor tissue are associated with longer survival among patients with glioblastoma who are receiving nitrosourea-based adjuvant chemotherapy.[17,18]

A pilot phase 2 trial demonstrated the feasibility of the concomitant administration of temozolomide with fractionated radiotherapy, followed by up to six cycles of adjuvant temozolomide, and suggested that this treatment had promising clinical activity (two-year survival rate, 31 percent).[19] The European Organisation for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada (NCIC) Clinical Trials Group therefore initiated a randomized, multicenter, phase 3 trial to compare this regimen with radiotherapy alone in patients with newly diagnosed glioblastoma.

METHODS

PATIENTS

Patients 18 to 70 years of age with newly diagnosed and histologically confirmed glioblastoma (World Health Organization [WHO] grade IV astrocytoma) were eligible for the study. Eligible patients had a WHO performance status of 2 or less and adequate hematologic, renal, and hepatic function (absolute neutrophil count, ≥1500 per cubic millimeter; platelet count, ≥100,000 per cubic millimeter; serum creatinine level, ≤1.5 times the upper limit of normal in the laboratory where it was measured; total serum bilirubin level, ≤1.5 times the upper limit of normal; and liver-function values, <3 times the upper limit of normal for the laboratory). Patients who were receiving corticosteroids had to receive a stable or decreasing dose for at least 14 days before randomization. All patients provided written informed consent, and the study was approved by the ethics committees of the participating centers.

STUDY DESIGN AND TREATMENT

Within six weeks after the histologic diagnosis of glioblastoma, we randomly assigned eligible patients to receive standard focal radiotherapy alone (the control group) or standard radiotherapy plus concomitant daily temozolomide, followed by adjuvant temozolomide. Randomization was performed at the EORTC Data Center, and patients were stratified according to WHO performance status, whether or not they had previously undergone debulking surgery, and the treatment center.[20] The assigned treatment had to begin within one week after randomization.

Radiotherapy consisted of fractionated focal irradiation at a dose of 2 Gy per fraction given once daily five days per week (Monday through Friday) over a period of six weeks, for a total dose of 60 Gy. Radiotherapy was delivered to the gross tumor volume with a 2-to-3-cm margin for the clinical target volume. Radiotherapy was planned with dedicated computed tomography (CT) and three-dimensional planning systems; conformal radiotherapy was delivered with linear accelerators with nominal energy of 6 MV or more, and quality assurance was performed by means of individual case reviews.[21]

Concomitant chemotherapy consisted of temozolomide (marketed as Temodal in Europe and Canada and Temodar in the United States; Schering-Plough) at a dose of 75 mg per square meter per day, given 7 days per week from the first day of radiotherapy until the last day of radiotherapy, but for no longer than 49 days. After a 4-week break, patients were then to receive up to six cycles of adjuvant temozolomide according to the standard 5-day schedule every 28 days. The dose was 150 mg per square meter for the first cycle and was increased to 200 mg per square meter beginning with the second cycle, so long as there were no hematologic toxic effects. Because continuous daily temozolomide can cause lymphocytopenia, with a possible increased risk of opportunistic infections, patients in the radiotherapy-plus-temozolomide group were to receive prophylaxis against *Pneumocystis carinii* pneumonia, consisting of either inhaled pentamidine or oral trimethoprim–sulfamethoxazole,[22] during concomitant treatment with radiotherapy plus temozolomide. Antiemetic prophylaxis with metoclopramide or a 5-hydroxytryptamine$_3$ antagonist was recommended before the initial doses of concomitant temozolomide and was required during the adjuvant five-day courses of temozolomide.

SURVEILLANCE AND FOLLOW-UP

The baseline examination included CT or magnetic resonance imaging (MRI), full blood counts and blood chemistry tests, and a physical examination that included the Mini–Mental State Examination (MMSE) and a quality-of-life questionnaire. During radiotherapy (with or without temozolomide), patients were to be seen every week. Twenty-one to 28 days after the completion of radiotherapy and every 3 months thereafter, patients underwent a comprehensive evaluation, including administration of the MMSE and the quality-of-life questionnaire and radiologic assessment of the tumor. During adjuvant temozolomide therapy, patients underwent a monthly clinical evaluation and a comprehensive evaluation at the end of cycles 3 and 6. Tumor progression was defined according to the modified WHO criteria as an increase in tumor size by 25 percent, the appearance of new lesions, or an increased need for corticosteroids.[23] When there was tumor progression or after two years of follow-up, patients were treated at the investigator's discretion, and the type of second-line therapy was recorded. Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0, with a score of 1 indicating mild adverse effects, a score of 2 moderate adverse effects, a score of 3 severe adverse effects, and a score of 4 life-threatening adverse effects.

STATISTICAL ANALYSIS

The primary end point was overall survival; secondary end points were progression-free survival, safety, and the quality of life. Overall survival and progression-free survival were analyzed by the Kaplan–Meier method, with use of two-sided log-rank statistics. This study had 80 percent power at a significance level of 0.05 to detect a 33 percent increase in median survival (hazard ratio for death, 0.75), assuming that 382 deaths occurred. All analyses were conducted on an intention-to-treat basis. The Cox proportional-hazards model was fitted to adjust for stratification factors and other confounding variables. Toxic effects are reported separately for the radiotherapy period, defined as extending from day 1 of radiotherapy until 28 days after the last day of radiotherapy, or until the first day of adjuvant temozolomide therapy. The adjuvant-therapy period was defined as extending from the first day of adjuvant temozolomide therapy until 35 days after day 1 of the last cycle of temozolomide. Findings with respect to the quality of life are not reported here.

ORGANIZATION OF THE TRIAL

The concept of the trial was developed by Dr. Stupp in collaboration with the EORTC Data Center, the EORTC Brain Tumor and Radiotherapy Groups, and the NCIC Clinical Trials Group, represented by Drs. Cairncross and Eisenhauer. The radiotherapy design and quality assurance were supervised by Dr. Mirimanoff. The trial was sponsored by the EORTC Brain Tumor and Radiotherapy Groups (trial 22981/26981) in Europe and the NCIC Clinical Trials Group (trial CE.3) in Canada. The trial was supported by an unrestricted educational grant from Schering-Plough, which also provided the study drug; however, Schering-Plough was not involved in trial design or analysis. All data were collected by the EORTC and NCIC data centers and reviewed by Drs. Stupp and Mirimanoff. The analysis was performed by the EORTC statistician, Mr. Gorlia. Histologic specimens were reviewed centrally (according to the revised WHO classification system[24]) by a panel of three neuropathologists in Europe (Robert C. Janzer in Lausanne, Switzerland [chair]; Peter Wesseling in Nijmegen, the Netherlands; and Karima Mohktari in Paris) and a single neuropathologist in Canada (Samuel Ludwin, Kingston, Ont.). The article was written by Dr. Stupp with support from a medical writer and coauthors; all authors reviewed the manuscript.

Table 1. Demographic Characteristics of the Patients at Baseline.

Characteristic	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
Age — yr		
Median	57	56
Range	23–71	19–70
Age — no. (%)*		
<50 yr	81 (28)	90 (31)
≥50 yr	205 (72)	197 (69)
Sex — no. (%)		
Male	175 (61)	185 (64)
Female	111 (39)	102 (36)
WHO performance status — no. (%)*†		
0	110 (38)	113 (39)
1	141 (49)	136 (47)
2	35 (12)	38 (13)
Extent of surgery — no. (%)*		
Biopsy	45 (16)	48 (17)
Debulking	241 (84)	239 (83)
Complete resection	113 (40)	113 (39)
Partial resection	128 (45)	126 (44)
Time from diagnosis to radiotherapy — wk		
Median	5	5
Range	2.0–12.9	1.7–10.7
Baseline MMSE score — no. (%)‡		
30	91 (32)	100 (35)
27–29	97 (34)	96 (33)
≤26	86 (30)	81 (28)
Data missing	12 (4)	10 (3)
Corticosteroid therapy — no. (%)		
Yes	215 (75)	193 (67)
No	70 (24)	94 (33)
Data missing	1 (<1)	0
Slides available for pathological review — no. (%)	246 (86)	239 (83)
Findings on pathological review — no. (%)		
Glioblastoma	229 (93)	221 (92)
Anaplastic astrocytoma§	9 (4)	7 (3)
Inconclusive material	3 (1)	3 (1)
Other	5 (2)	8 (3)

* This characteristic was used as a stratification factor at the time of randomization.
† A performance status of 0 denotes asymptomatic, 1 symptomatic and fully ambulatory, and 2 symptomatic and in bed less than 50 percent of the day.
‡ The maximum score on the Mini–Mental State Examination (MMSE) is 30, and scores above 26 are considered to indicate normal mental status.
§ Anaplastic astrocytoma included oligoastrocytoma.

RESULTS

PATIENTS

From August 2000 until March 2002, 573 patients from 85 institutions in 15 countries were randomly assigned to receive radiotherapy (286 patients) or radiotherapy plus temozolomide (287 patients). Nearly 50 percent of the patients were enrolled at 17 institutions. The characteristics of the patients in the two groups were well balanced at baseline (Table 1). The median age was 56 years, and 84 percent of patients had undergone debulking surgery. Slightly more patients in the radiotherapy group than in the radiotherapy-plus-temozolomide group were receiving corticosteroids at the time of randomization (75 percent vs. 67 percent). Histologic slides were submitted for 85 percent of patients, and central pathological review confirmed the diagnosis of glioblastoma in 93 percent of the reviewed cases; 3 percent had anaplastic astrocytoma or oligoastrocytoma (WHO grade III), and in 1 percent submitted material was insufficient for a definitive diagnosis.

DISPOSITION OF PATIENTS AND DELIVERY OF TREATMENT

The median time from diagnosis to the start of therapy was 5 weeks (range, 2.0 to 12.9) in the radiotherapy group and 5 weeks (range, 1.7 to 10.7) in the radiotherapy-plus-temozolomide group. Table 2 summarizes the details of treatment. Unplanned interruptions in radiotherapy were usually brief (median, four days) and interruptions due to the toxicity of therapy occurred in only 3 percent of the radiotherapy group and 4 percent of the radiotherapy-plus-temozolomide group. The other reasons were mainly administrative (e.g., holidays, radiotherapy equipment maintenance, or technical problems). One patient randomly assigned to radiotherapy alone received radiotherapy plus temozolomide. Among the 287 patients who were assigned to receive concomitant radiotherapy plus temozolomide, 85 percent completed both radiotherapy and temozolomide as planned. Thirty-seven patients (13 percent) prematurely discontinued temozolomide because of toxic effects (in 14 patients), disease progression (in 11), or other reasons (in 12).

After radiotherapy, 223 patients in the radiotherapy-plus-temozolomide group (78 percent) started adjuvant temozolomide and received a median of 3 cycles (range, 0 to 7); 47 percent of patients completed 6 cycles. The main reason for not

Table 2. Disposition of Patients and Intensity of Treatment.

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
Radiotherapy		
Never started radiotherapy — no. (%)	7 (2)	3 (1)
Dose — Gy		
Median	60	60
Range	12–62	12–62
No. of fractions		
Median	30	30
Range	6–33	5–33
Duration — wk		
Median	6.1	6.0
Range	1.3–7.6	0.6–10.3
Interruption or delay in radiotherapy — no. (%)	78 (27)	92 (32)
Delay due to toxicity — no. (%)	8 (3)	12 (4)
Received ≤90% of planned dose — no. (%)	22 (8)	14 (5)
Early discontinuation of radiotherapy — no. (%)	19 (7)	14 (5)
Reason for discontinuation — no. (%)		
Disease progression	17 (6)	11 (4)
Other*	2 (1)	3 (1)
Concomitant temozolomide		
Never started concomitant temozolomide — no. (%)	—	6 (2)
Duration of therapy — days		
Median	—	42
Range	—	40–55
Received ≤90% of planned dose — no. (%)	—	23 (8)
Early discontinuation of concomitant temozolomide — no. (%)	—	37 (13)
Reason for discontinuation of temozolomide — no. (%)		
Toxic effects	—	14 (5)
Disease progression	—	11 (4)
Other*	—	12 (4)
Adjuvant-therapy period		
Adjuvant temozolomide started — no. (%)		223 (78)
Cycles of temozolomide		
Median	—	3
Range	—	0–7
Patients completing 6 cycles — no. (%)	—	105 (47)
Dose escalated to 200 mg/m² at cycle 2 — no. (%)	—	149 (67)
Adjuvant temozolomide discontinued — no. (%)		118 (53)
Reason for discontinuation — no. (%)		
Disease progression	—	86 (39)
Toxic effects	—	17 (8)
Decision by patient	—	8 (4)
Other	—	6 (3)
Missing data	—	1 (<1)

* Other reasons included any missed dose or patient or prescription error.

beginning or not completing adjuvant temozolomide therapy was disease progression. Only 8 percent of patients discontinued adjuvant temozolomide because of toxic effects. Beginning with cycle 2, the dose of temozolomide was increased to 200 mg per square meter in 67 percent of patients. Only 9 percent of patients did not receive the higher dose because of hematologic toxicity.

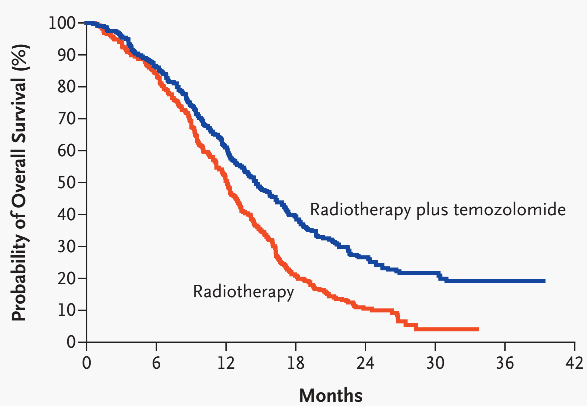
SURVIVAL AND PROGRESSION

At a median follow-up of 28 months, 480 patients (84 percent) had died. The unadjusted hazard ratio for death in the radiotherapy-plus-temozolomide group as compared with the radiotherapy group was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001 by the log-rank test). These data indicate a 37 percent relative reduction in the risk of death for patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone.

The median survival benefit was 2.5 months; the median survival was 14.6 months (95 percent confidence interval, 13.2 to 16.8) with radiotherapy plus temozolomide and 12.1 months (95 percent confidence interval, 11.2 to 13.0) with radiotherapy alone (Fig. 1 and Table 3). The two-year survival rate was 26.5 percent (95 percent confidence interval, 21.2 to 31.7 percent) in the group given radiotherapy plus temozolomide, as compared with 10.4 percent (95 percent confidence interval, 6.8 to 14.1 percent) with radiotherapy alone. The median progression-free survival was 6.9 months (95 percent confidence interval, 5.8 to 8.2) with radiotherapy plus temozolomide and 5.0 months (95 percent confidence interval, 4.2 to 5.5) with radiotherapy alone (hazard ratio for death or disease progression, 0.54 [95 percent confidence interval, 0.45 to 0.64]; P<0.001 by the log-rank test) (Fig. 2).

The hazard ratio for death was adjusted by fitting the Cox proportional-hazard models. In addition to the stratification factors (the extent of surgery, WHO performance status, and treatment center), other possible confounding factors — age, use or nonuse of corticosteroids at randomization, sex, score on the MMSE, and tumor location — were included. The adjusted hazard ratio for death in the radiotherapy-plus-temozolomide group as compared with the radiotherapy group — 0.62 (95 percent confidence interval, 0.51 to 0.75) — was essentially the same as the unadjusted hazard ratio.

Survival according to prognostic factors, including age, sex, extent of surgery, WHO performance status, and use or nonuse of corticosteroids, was also analyzed (see Table 1 in the Supplementary Appendix, available with the full text of this article at www.nejm.org). Radiotherapy plus temozolomide was associated with a significant improvement in median overall survival in nearly all subgroups of patients (see Fig. 1 in the Supplementary Appendix); the exceptions were the small subgroup of 93 patients who underwent biopsy only and the 70 patients with a poor performance status.



No. at Risk							
Radiotherapy	286	240	144	59	23	2	0
Radiotherapy plus temozolomide	287	246	174	109	57	27	4

Figure 1. Kaplan–Meier Estimates of Overall Survival According to Treatment Group.

The hazard ratio for death among patients treated with radiotherapy plus temozolomide, as compared with those who received radiotherapy alone, was 0.63 (95 percent confidence interval, 0.52 to 0.75; P<0.001).

SAFETY

We analyzed adverse events separately during radiotherapy (with or without concomitant temozolomide), the adjuvant-therapy period, and the entire study period (from study entry until disease progression or last follow-up). No grade 3 or 4 hematologic toxic effects were observed in the radiotherapy group. During concomitant temozolomide therapy, grade 3 or 4 neutropenia was documented in 12 patients (4 percent), and grade 3 or 4 thrombocytopenia occurred in 9 patients (3 percent) (Table 4). Overall, 19 patients (7 percent) had any type of grade 3 or 4 hematologic toxic effect. During adjuvant temozolomide therapy, 14 percent of patients had any grade 3 or 4 hematologic toxic effect, 4 percent had grade 3 or 4 neutropenia, and 11 percent had grade 3 or 4 thrombocytopenia.

During the radiotherapy period, severe infections occurred in 6 patients in the radiotherapy group (2 percent) and in 9 patients in the radiotherapy-plus-temozolomide group (3 percent); during adjuvant temozolomide therapy, 12 patients (5 percent) had severe infections. The most common nonhematologic adverse event during radiotherapy was moderate-to-severe fatigue in 26 percent of patients in the radiotherapy group and 33 percent in the radiotherapy-plus-temozolomide group (Table 2 in the Supplementary Appendix). Thromboembolic events occurred in 28 patients (5 percent) — 16 in the radiotherapy group and 12 in the radiotherapy-plus-temozolomide group. Two patients in the radiotherapy-plus-temozolomide group died of cerebral hemorrhage in the absence of a coagulation disorder or thrombocytopenia. Pneumonia was reported in five patients in the radiotherapy group and three in the radiotherapy-plus-temozolomide group. Opportunistic infections occurred in two patients; one patient treated with radiotherapy alone had suspected *P. carinii* pneumonia, and one patient in the radiotherapy-plus-temozolomide group had proven bacterial and candida pneumonia.

TREATMENT AFTER DISEASE PROGRESSION

If disease progression occurred, further treatment was at the physician's discretion. At the cutoff date (May 10, 2004), 512 patients — 268 in the radiotherapy group (94 percent) and 244 in the radiotherapy-plus-temozolomide group (85 percent) — had disease progression. At the time of progression, 23 percent of patients in both treatment groups underwent a second surgery, and 72 percent of patients in the radiotherapy group and 58 percent in the radiotherapy-plus-temozolomide group received chemotherapy. Salvage chemotherapy consisted of temozolomide in 60 percent of patients in the radiotherapy group and 25 percent of patients in the radiotherapy-plus-temozolomide group. The response to salvage chemotherapy was not recorded as part of our study.

DISCUSSION

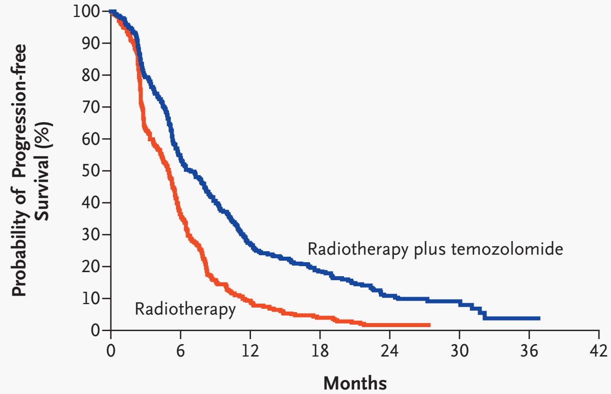
For more than 30 years, chemotherapy given as an adjunct to radiotherapy or before radiotherapy has been widely investigated in patients with malignant glioma. Such treatment has had limited success.[6-8,10,25-27] The present study demonstrates that the addition of chemotherapy to radiotherapy significantly prolongs survival among patients with newly diagnosed glioblastoma, with a median increase in survival of 2.5 months or a relative reduction in the risk of death of 37 percent. Unlike most previous studies, which included patients with both glioblastoma (WHO grade IV) and anaplastic astrocytoma (WHO grade III), who have a better prognosis, our study was designed to include only patients with glioblastoma. At two years, we found a clinically meaningful increase — by a factor of 2.5 — in the survival rate, from 10 percent with radiotherapy alone to 27 percent with radiotherapy plus temozolomide, consistent with the findings of the preceding phase 2 trial.[19] An exploratory analysis of subgroups defined according to known prognostic factors demonstrated a survival benefit in nearly all subgroups.

The outcome for patients treated with radiotherapy alone in our trial compares favorably with the outcome in other trials.[9,11,28] Patients being treated with corticosteroids received stable or decreasing doses before randomization and started radiotherapy within one week after randomization. These cri-

Table 3. Overall and Progression-free Survival According to Treatment Group.*

Variable	Radiotherapy (N=286)	Radiotherapy plus Temozolomide (N=287)
	value (95% CI)	
Median overall survival (mo)	12.1 (11.2–13.0)	14.6 (13.2–16.8)
Overall survival (%)		
At 6 months	84.2 (80.0–88.5)	86.3 (82.3–90.3)
At 12 months	50.6 (44.7–56.4)	61.1 (55.4–66.7)
At 18 months	20.9 (16.2–26.6)	39.4 (33.8–45.1)
At 24 months	10.4 (6.8–14.1)	26.5 (21.2–31.7)
Median progression-free survival (mo)	5.0 (4.2–5.5)	6.9 (5.8–8.2)
Progression-free survival (%)		
At 6 months	36.4 (30.8–41.9)	53.9 (48.1–59.6)
At 12 months	9.1 (5.8–12.4)	26.9 (21.8–32.1)
At 18 months	3.9 (1.6–6.1)	18.4 (13.9–22.9)
At 24 months	1.5 (0.1–3.0)	10.7 (7.0–14.3)

* A total of 160 patients in the radiotherapy group and 60 patients in the radiotherapy-plus-temozolomide group received temozolomide as salvage therapy. CI denotes confidence interval.



No. at Risk							
Radiotherapy	286	104	26	11	4	0	0
Radiotherapy plus temozolomide	287	154	77	51	24	8	1

Figure 2. Kaplan–Meier Estimates of Progression-free Survival According to Treatment Group.

The hazard ratio for death or disease progression among patients treated with radiotherapy plus temozolomide, as compared with those treated with radiotherapy alone, was 0.54 (95 percent confidence interval, 0.45 to 0.64; P<0.001).

Table 4. Grade 3 or 4 Hematologic Toxic Effects in Patients Treated with Temozolomide.

Toxic Effect	Concomitant Temozolomide Therapy (N=284)	Adjuvant Temozolomide Therapy (N=223)	Entire Study Period* (N=284)
	number of patients (percent)		
Leukopenia	7 (2)	11 (5)	20 (7)
Neutropenia	12 (4)	9 (4)	21 (7)
Thrombocytopenia	9 (3)	24 (11)	33 (12)
Anemia	1 (<1)	2 (1)	4 (1)
Any	19 (7)	32 (14)	46 (16)

* The entire study period was defined as the period from study entry to seven days after disease progression.

teria may have served to exclude patients with the worst prognosis, who may not benefit from any therapy. Moreover, most patients had undergone debulking surgery. The relatively long survival after disease progression (approximately seven months in both groups) is also noteworthy. This extended survival may reflect either patient selection or the early detection of tumor progression by means of regular radiographic assessment. Furthermore, 72 percent of patients in the radiotherapy group and 58 percent of patients in the radiotherapy-plus-temozolomide group received salvage chemotherapy at the time of progression.

This trial was designed to determine whether the addition of temozolomide to radiotherapy early in the course of treatment prolongs survival among patients with glioblastoma, but it was not designed to distinguish between the effects of concomitant therapy with radiotherapy plus temozolomide and adjuvant treatment with temozolomide. At the time the trial was conceived, it was deemed most important to administer chemotherapy early in the course of the disease, for a sufficiently long time, and concurrently with radiotherapy. Temozolomide was given concomitantly with radiotherapy on a continuous schedule for several reasons. First, daily administration of low doses makes possible an increase by almost a factor of two in dose intensity, as compared with the standard regimen, without an increase in toxicity.[15] Second, continuous administration of an alkylating agent depletes MGMT,[16] an enzyme that may be induced by radiotherapy and that is necessary for repair of damage to DNA caused by alkylating agents.[29] In a companion translational study also reported in this issue of the *Journal*, we observed that methylation of the *MGMT* promoter, which results in gene silencing, is associated with a striking survival benefit in patients treated with radiotherapy plus temozolomide.[30] Third, synergy between temozolomide and radiotherapy has been observed in vitro.[31-33] The spontaneous conversion of temozolomide into the active metabolite and its ability to cross the blood–brain barrier also favors this regimen.[34] Finally, to ensure sufficient exposure to the drug, we added six cycles of adjuvant temozolomide after the completion of radiotherapy.

In the context of palliative care, chemotherapy-induced toxic effects should be manageable. Nausea was controlled with standard antiemetic agents. Severe myelosuppression was observed in 16 percent of patients, leading to the early discontinuation of chemotherapy in 5 percent. Whether the addition of chemotherapy increases the risk of radiotherapy-induced cognitive deficits cannot be assessed at this time. However, long-term monitoring and observational studies of late toxic effects will be important to guide treatment recommendations in the future. Furthermore, prolonged chemotherapy with alkylating agents has been associated with myelodysplastic syndromes and secondary leukemia occurring years after therapy.[35] In our trial, at a median follow-up of approximately two years, there had been no evidence of any increase in treatment-induced late toxic effects. Such late toxicity may become a greater concern, however, if this regimen is used in patients with intermediate- or low-grade glioma, who have a more favorable prognosis in terms of survival.

In conclusion, the addition of temozolomide to radiotherapy early in the course of glioblastoma provides a statistically significant and clinically meaningful survival benefit. Nevertheless, the challenge remains to improve clinical outcomes further. For this reason, the regimen of radiotherapy plus temozolomide should serve as the new platform from which to explore innovative regimens for treating malignant gliomas. Many questions remain unanswered regarding the applications of this regimen to lower grade gliomas and the optimal combination of radiotherapy and temozolomide.

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APPENDIX

The following institutions and investigators participated in the trial: EORTC — Algemeen Ziekenhuis Middelheim, Antwerp, Belgium (D. Van Den Weyngaert); Klinikum Aschaffenburg, Germany (S. Kaendler); Nervenklink, Bamberg, Germany (P. Krauseneck); Hospital Clinico y Provincial de Barcelona, Barcelona, Spain (N. Vinolas); Institut Catala D'Oncologia, Barcelona, Spain (S. Villa); Universitaetsklinikum (Charité)–Humboldt–Universität, Berlin (R.E. Wurm); Centre Hospitalier Régional de Besançon–Hopital Jean Minjoz, Besançon, France (M.-H. Baron Maillot); Ospedale Bellaria, Bologna, Italy (F. Spagnolli); Institut Bergonie, Bordeaux, France (G. Kantor); Centre Hospitalier Universitaire de Brest, Brest, France (J.-P. Malhaire); Cliniques Universitaires St. Luc, Brussels (L. Renard); Hopital Universitaire Erasme, Brussels (O. De Witte); Ospedale Sant Anna, Como, Italy (L. Scandolaro); Medisch Centrum Haaglanden–Westeinde, Den Haag, the Netherlands (C.J. 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