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CLINICAL STUDY – PATIENT STUDY

Radiotherapy followed by adjuvant temozolomide with or without neoadjuvant ACNU-CDDP chemotherapy in newly diagnosed glioblastomas: a prospective randomized controlled multicenter phase III trial

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Abstract A prospective randomized controlled multicenter phase III trial was conducted to evaluate the effects of neoadjuvant chemotherapy with nimustine (ACNU)-cisplatin (CDDP) when used in conjunction with radiotherapy plus adjuvant temozolomide in patients with newly diagnosed glioblastoma. The study population was randomly assigned into one treatment and one control group. Both groups received radiotherapy followed by six cycles of adjuvant oral temozolomide (150–200 mg/m^2) for 5 days every 28 days after surgery. Prior to radiotherapy, the treatment group also received two cycles, 6 weeks apart, of neoadjuvant chemotherapy with ACNU (40 mg/m^2/day) and CDDP (40 mg/m^2/day) infused continuously for 72 h. The primary end-point was median survival time. The study has closed after interim analysis with a total of 82 patients (48.8% of target number) due to unacceptable

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high frequency of toxicity profiles in spite of the promising actuarial survival outcome. Median survival time was 28.4 months [90% confidence interval (CI), 21.1 months to not available] in the treatment group and 18.9 months (90% CI, 17.1–27.4 months) in the control group ($P = 0.2$). The 2-year survival rate and progression-free survival time were 50.9% and 6.6 months (90% CI, 3.5–9.5 months) in the treatment group and 27.8% and 5.1 months (90% CI, 3.8–8.8 months) in the control group. Grade 3 or 4 toxicity was documented in 26 (68.4%) patients in the treatment group, including three neutropenic fever and one death from sepsis, while grade 3 or 4 toxicity occurred in 6 patients (15.8%) in the control group. The high frequency of serious hematological toxicity with ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy and adjuvant temozolomide limits its usage as primary treatment for glioblastoma. Future studies should aim to identify a subpopulation at reduced risk for ACNU-CDDP toxicity so that the potential of this protocol can be realized.

Keywords Glioblastoma · Neoadjuvant chemotherapy · ACNU-CDDP · Temozolomide · Toxicity

Introduction

Glioblastoma is the most common glial tumor and remains a therapeutic challenge in spite of the various strategies and clinical trials that have been introduced over the past few decades. However, management of malignant glioma is entering a new era of hope, because the unraveling of its molecular characteristics has led to novel chemotherapeutic agents with diverse applications that include multidisciplinary approaches. Use of temozolomide has recently become a standard treatment for patients with glioblastoma [1]. Although its effects have fallen short of expectations, the ease of use and low toxicity of this novel agent have changed the strategy of later studies, which now focus on combining temozolomide with other drugs [2, 3].

Before the temozolomide era and in addition to radiotherapy, nitrosourea compounds, such as nimustine (ACNU) or carmustine (BCNU), were the core drugs used for management of malignant gliomas [2]. These drugs were usually used with hydrophilic agents such as cisplatin (CDDP) to increase its anticancer effect [4]. The authors also had reported several protocols using ACNU and CDDP for treatment of glioblastoma, and reported the efficacy and feasibility of their usage as neoadjuvant chemotherapy [5–7]. In this study, we developed a new protocol of neoadjuvant ACNU-CDDP chemotherapy followed by radiotherapy and adjuvant temozolomide for newly diagnosed glioblastoma patients after surgery. To confirm the benefit of the neoadjuvant ACNU-CDDP chemotherapy and to evaluate the additive effect of temozolomide in patients with newly diagnosed glioblastoma, we performed this prospective randomized controlled multicenter phase III trial.

The trial started to enroll patients on 1 August 2005 with a target number of 168 patients. However, enrollment was stopped after recruitment of 82 patients on 31 December 2007. Enrollment ceased after interim analysis revealed a frequency of toxicity related to the neoadjuvant chemotherapeutic agents that is not acceptable in modern cancer management. Herein, we report the overall results of the trial in detail.

Patients and methods

Patients and eligibility

This trial was a multicenter, open-label phase III study of adult glioblastoma patients from an alliance of five institutes that are collectively known as the Seoul Clinical Neuro-Oncology Group (SCNOG). The study protocol was approved by each of the ethics committees of the participating institutes. All patients gave written informed consent. Patients who were 15–70 years of age with newly diagnosed supratentorial glioblastoma after histological confirmation [World Health Organization (WHO) grade IV astrocytoma] were eligible for the study. Inclusion criteria included good performance status (Karnofsky performance score of 70 or higher) as well as adequate hematologic, renal, and hepatic function (absolute neutrophil count, $\geq$1,500/mm^3; platelet count, $\geq$100,000/mm^3; serum creatinine level, $\leq$1.7 mg/dl; total serum bilirubin level, $\leq$2.0 mg/dl; and liver function values, <2.5 times the upper limit of normal in the laboratory where it was measured).

Study design and treatment

The study population was randomly assigned to either the treatment group or control group. The estimated sample size was 168 patients (84 for each group) hypothesizing a 6-month survival gain for the treatment group compared with the median survival time of 12 months for the control group using a level of significance of 10% and power of 80% [8]. Randomization was performed at the Medical Research Collaborating Center (MRCC) at the Seoul National University Hospital stratified by age (cutoff value 50 years), extent of resection [complete or not, determined by residual enhancing lesions in magnetic resonance (MR) images performed within 48 h after surgery], and institute. The assigned treatment had to begin within 2 weeks after randomization.

The control group received standard conventional radiotherapy followed by six cycles of adjuvant temozolomide. Radiotherapy consisted of fractionated focal irradiation at dose of 1.8–2.0 Gy per fraction given once daily over a period of 6 weeks, which falls under a total dose of 60.0–61.2 Gy to the gross tumor volume, with a 2–3-cm margin for the clinical target volume. Radiotherapy was planned with dedicated computed tomography and three-dimensional planning systems. Conformal radiotherapy was delivered with linear accelerators with nominal energy of 4 MV or more. Four weeks after the end of the radiotherapy treatment, patients received up to six cycles of adjuvant oral temozolomide (150–200 mg/m^2) for 5 days every 28 days.

The treatment group received two cycles of ACNU-CDDP neoadjuvant chemotherapy, followed by radiotherapy and six cycles of adjuvant temozolomide. The neoadjuvant chemotherapy with ACNU (40 mg/m^2/day) and CDDP (40 mg/m^2/day) was administered by continuous infusion for 72 h and was repeated after 6 weeks. However, the second cycle of ACNU-CDDP chemotherapy was delayed for up to 10 weeks unless laboratory findings met the hematologic criteria (absolute neutrophil count, $\geq$1,500/mm^3; platelet count, $\geq$100,000/mm^3; serum creatinine level, $\leq$1.7 mg/dl) or nonhematologic criteria [$\leq$ National Cancer Institute Common Terminology Criteria Adverse Events (NCI CTCAE, version 3.0) grade 1]. Additionally, the dose of ACNU-CDDP was reduced to 75% of the dose administered in the previous cycle if hematologic toxicities (absolute neutrophil count, <100/mm^3; absolute neutrophil count, <500/mm^3; platelet count, <100,000/mm^3) developed for more than 1 week during the first cycle of ACNU-CDDP chemotherapy. Radiotherapy had to be initiated 6 weeks after the last cycle of ACNU-CDDP chemotherapy, and adjuvant temozolomide was administered in the same manner as in the control group.

Surveillance and follow-up

The baseline examination included MR imaging, full blood counts, blood chemistry tests, and a physical examination. Before the first cycle of neoadjuvant chemotherapy, patients underwent a comprehensive evaluation, which included audiometry. During ACNU-CDDP chemotherapy, patients were seen every 2 weeks, and MR imaging was performed at 6 weeks after the initiation of the first cycle and at 6 weeks after the completion of the second cycle. During radiotherapy, patients were seen every week. Six weeks after the completion of radiotherapy, patients underwent a comprehensive evaluation, including a radiologic assessment of the tumor. During adjuvant temozolomide therapy, patients underwent a monthly clinical evaluation and were subjected to MR imaging at the end of cycles 3 and 6, and every 3 months thereafter.

The assessment of radiological outcome was defined as previously described [5]. Briefly, complete response was defined as absence of enhancement lesion, while partial response was defined as >50% decrease in maximum cross-sectional area of enhancement lesion of tumor. Progressive disease was defined as increase in tumor size by 25%, appearance of new lesions, or increased need for corticosteroids.

If disease progression was confirmed during the treatment, the next phase of the treatment protocol was performed; for example, if progression occurred after the first cycle of ACNU-CDDP neoadjuvant chemotherapy, the patient was treated with radiotherapy skipping the rest of the cycles and followed by adjuvant temozolomide. When disease progression occurred during or after the adjuvant temozolomide, these patients were defined as censored, and a secondary treatment was administered such as gamma knife radiosurgery, reoperation, or salvage chemotherapy at the discretion of the treating physician. Toxic effects were graded in accordance with the NCI CTCAE, version 3.0.

Statistical analysis

The primary end-point was median survival time, and secondary end-points were progression-free survival and safety. Survival analysis was performed via the Kaplan–Meier method with one-sided log-rank statistics using 80% power at significance level of 0.10. All analyses were carried out on an intention-to-treat (ITT) and per-protocol (PP) basis. Patients were included in the PP analysis only when they had completed the protocol past three or more cycles of adjuvant temozolomide without any major protocol violation. Fisher's exact test was used to compare the categorical variables, and Student's *t*-test was used to compare the continuous variables between the two groups. All statistical analyses were performed using SAS® version 9.1.3 [SAS Institute (Korea) Inc.] by MRCC.

Results

Patient characteristics

From August 2005 to December 2007, a total of 82 (48.8% of target enrollment number) patients from five institutes were randomly assigned to either treatment group (40 patients) or control group (42 patients). Among them, six patients did not meet the inclusion criteria and therefore were excluded from the analysis. Thus, 76 patients (38 for each group) were analyzed for overall survival and

progression-free survival. The baseline characteristics of the patients in the two groups were well balanced except for extent of resection (Table 1). A total of 35 (42.7%) patients were suitable for the PP set without any biased distribution [18 (45.0%) patients in the treatment group, 17 (40.5%) in the control group].

Survival and response

At time of analysis, 51 (62.2%) patients were alive and 31 (37.8%) patients had died. In the ITT analysis, median survival was 28.4 months (90% CI, 21.1 months to not available) in the treatment group and 18.9 months (90% CI, 17.1–27.4 months) in the control group (Fig. 1a and Table 2). Although the median survival benefit in the treatment group over the control group was 9.5 months, this difference did not reach statistical significance ($P = 0.2$). The 1- and 2-year survival rates were 72.4% and 50.9%, respectively, in the treatment group, and 81.7% and 27.8%, respectively, in the control group. In the PP analysis, the treatment group was estimated to have significantly longer survival time than the control group ($P < 0.001$), although median survival time was not estimated in the treatment group due to heavy censoring (Fig. 1b and Table 2). In terms of progression-free survival, there was no statistically significant difference between the two groups in either the ITT analysis or the PP analysis (Fig. 2 and Table 2).

Safety

All adverse events that occurred during each treatment phase are summarized in Table 3. During the ACNU-CDDP neoadjuvant chemotherapy period, 25 (65.8%) patients experienced grade 3 or 4 adverse effects, most of which were hematological toxicities, including three patients who experienced neutropenic fever and one patient who died from sepsis. A total of 25 patients (65.8%) of the treatment group could complete both cycles of ACNU-CDDP without delay of schedule, although seven patients had to reduce the dose according to the safety criteria. The reasons for discontinuation of ACNU-CDDP treatment in the last 13 patients of the treatment group were toxicity in three patient including one death, and disease progression

Table 1 Demographic characteristics of the patients

Characteristics	Radiotherapy plus adjuvant temozolomide group ($N = 42$)	ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus adjuvant temozolomide group ($N = 40$)	P value*
Mean age (years)	51.1 ± 11.8	51.4 ± 12.4	
Age (years), *n* (%)			0.9
<50	19 (45.2)	16 (40.0)	
≥50	23 (54.8)	24 (60.0)	
Gender, *n* (%)			0.5
Male	15 (35.7)	11 (27.5)	
Female	27 (64.3)	29 (72.5_	
Resection, *n* (%)			0.03
Complete	17 (40.5)	13 (32.5)	
Incomplete	12 (28.6)	22 (55.0)	
Biopsy	13 (31.0)	5 (12.5)	
Site, *n* (%)			0.5
A	0 (0.0)	2 (5.0)	
B	4 (9.5)	2 (5.0)	
C	3 (7.1)	1 (2.5)	
D	5 (11.9)	7 (17.5)	
E	30 (71.4)	28 (70.0)	
Disposition of patients, *n* (%)			0.4
Enrollment error	4 (9.5%)	2 (5.0)	
Cutoff for analysis	6 (14.3)	10 (25.0)	
Completion of study	32 (76.2)	28 (70.0)	
Per-protocol, *n* (%)**			0.8
No	25 (59.5)	22 (55.0)	
Yes	17 (40.5)	18 (45.0)	

*Fisher's exact test or Student's *t*-test

**Patients were included in the per-protocol analysis only when they underwent three or more cycles of adjuvant temozolomide and no major protocol violation had occurred

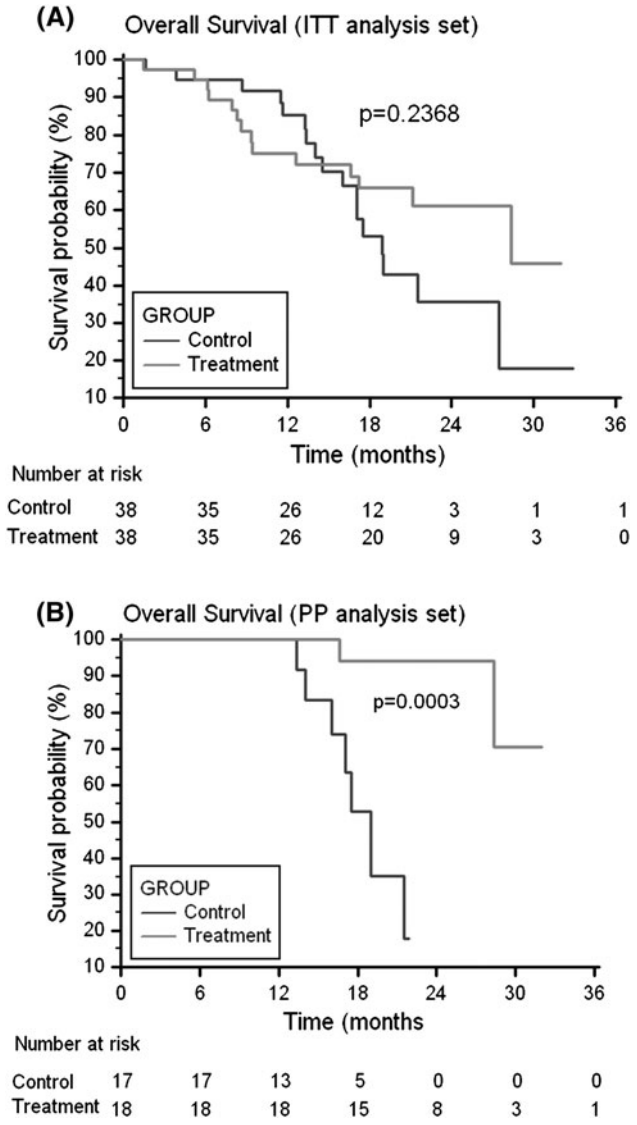

Fig. 1 Kaplan-Meier estimates of overall survival according to treatment group. **a** According to the results of the ITT analysis, median survival was 28.4 months (90% CI, 21.1 months to not available) for the ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus temozolomide group and 18.9 months (90% CI, 17.1–27.4 months) for the radiotherapy plus temozolomide group. **b** In the PP analysis, the treatment group had significantly longer survival time than the control group ($P < 0.001$); median survival time was not estimated in the treatment group due to heavy censoring (90% CI, 28.4 months to not available) and was 19.0 months (90% CI, 17.1–21.5 months) in the control group

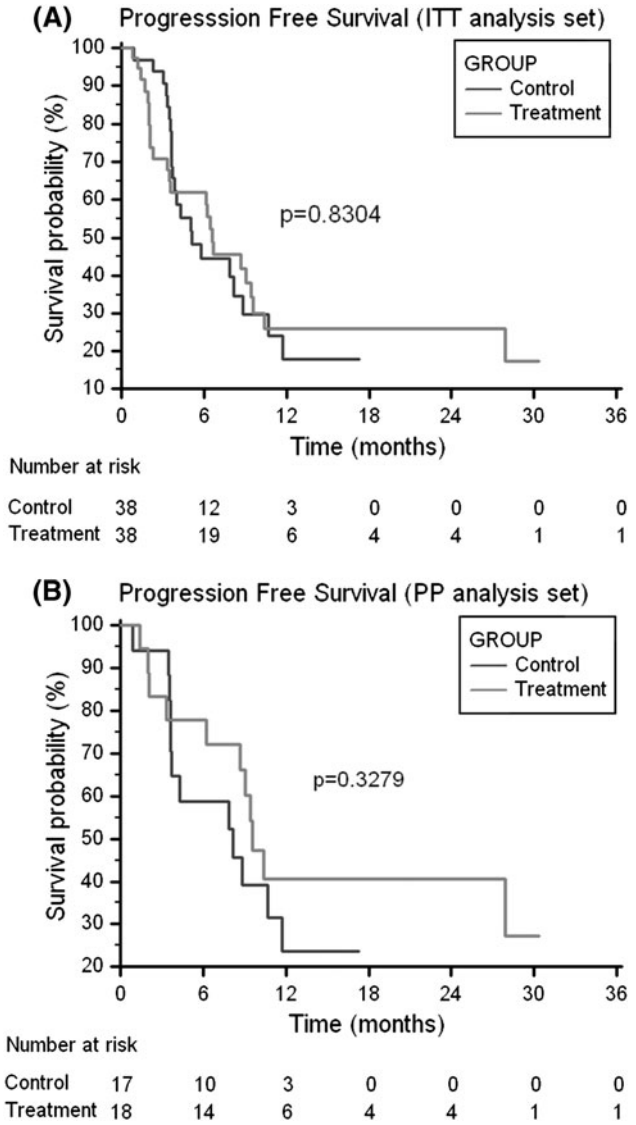

Fig. 2 Kaplan–Meier estimates of progression-free survival according to treatment group. The progression-free survival rate was superior in the ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus adjuvant temozolomide group compared with the radiotherapy plus temozolomide group in both the ITT analysis (**a**) and PP analysis (**b**) [6.6 months (90% CI, 3.5–9.5 months) and 5.1 months (90% CI, 3.8–8.8 months); 9.6 months (90% CI, 8.7–27.9 months) and 8.2 months (90% CI, 3.7–11.7 months), respectively]. However, all differences failed to reach statistical significance ($P = 0.8$ and $P = 0.3$, respectively)

in others. Without those three patients who could not complete the ACNU-CDDP treatment due to toxicity, the other 22 patients with grade 3 or 4 toxicity recovered after conservative management within expected schedule. There was a relatively lower rate of serious toxicities during the radiotherapy phase (four patients in the control group and two patients in the treatment group) and the temozolomide phase (two patients in each group).

Secondary treatment after disease progression

A total of 31 patients [21 (55.3%) in the control group, 10 (26.3%) in the treatment group] received a secondary treatment due to disease progression. The patients in the control group were treated with a subsequent treatment after disease progression more frequently than were patients in the treatment group. The details of the secondary treatments are summarized in Table 4.

Table 2 Overall and progression-free survival according to treatment group

	Overall survival				Progression-free survival			
	ITT[a]		PP[b]		ITT		PP	
	Control[c]	Treatment[d]	Control	Treatment	Control	Treatment	Control	Treatment
Median (months)	18.9	28.4	19.0	NA	5.1	6.6	8.2	9.6
90% CI for median (months)	17.1–27.4	21.1–NA*	17.1–21.5	28.4–NA	3.8–8.8	3.5–9.5	3.7–11.7	8.7–27.9
P value**	0.2		<0.001		0.8		0.3	
Censored, *n* (%)	21 (55.3)	24 (63.2)	10 (58.8)	16 (88.9)	16 (42.1)	14 (36.8)	5 (29.4)	7 (38.9)

[a] Intention-to-treat

[b] Per-protocol

[c] The radiotherapy plus adjuvant temozolomide group

[d] The ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus temozolomide group

* Not available

** Log-rank test using level of significance of 0.10

Table 3 Treatment-related toxicities of NCI CTCAE grade 3 or 4

	Radiotherapy plus adjuvant temozolomide group ($N = 38$), *n* (%)			ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus adjuvant temozolomide group ($N = 38$), *n* (%)			
	RTx[a]	TMZ[b]	Total	ACNU-CDDP[c]	RTx	TMZ	Total
Hematologic							
Neutropenia				5 (13.2)	1 (2.6)		6 (15.8)
Thrombocytopenia	1 (2.6)		1 (2.6)	6 (15.8)			6 (15.8)
Anemia							
Any[d]				12 (31.6)		1 (2.6)	13 (34.2)
Nonhematologic							
Hepatotoxicity		1 (2.6)	1 (2.6)	2 (5.2)			2 (5.2)
Headache	1 (2.6)	1 (2.6)	2 (5.2)				
Dysuria	1 (2.6)		1 (2.6)				
Hemiparesis	1 (2.6)		1 (2.6)				
Otorrhea					1 (2.6)		1 (2.6)
Cardiovascular						1 (2.6)	1 (2.6)

[a] The radiotherapy phase

[b] The adjuvant temozolomide phase

[c] The ACNU-CDDP neoadjuvant chemotherapy phase

[d] including three cases of neutropenic fever and one death from sepsis

Table 4 Subsequent treatment after disease progression

	Radiotherapy plus adjuvant temozolomide group ($N = 38$), *n* (%)	ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy plus adjuvant temozolomide group ($N = 38$), *n* (%)
Yes	21 (55.3)	10 (26.3)
Bevacizumab-CPT-11	2 (5.2)	3 (7.9)
ACNU-CDDP	3 (7.9)	0
PCV[a]	9 (23.7)	5 (13.2)
Other agents	1 (2.6)	1 (2.6)
Gamma knife radiosurgery	6 (15.8)	1 (2.6)

[a] Procarbazine, lomustine, and vincristine

Discussion

Among the alkylating agents, nitrosourea compounds such as ACNU, BCNU, and lomustine (CCNU) have been mainstay agents for adjuvant or neoadjuvant treatment of malignant gliomas. Importantly, meta-analyses have confirmed the anticancer effects of nitrosourea compounds, which include survival benefits [9, 10]. The recent introduction of another new oral alkylating agent, temozolomide, enabled a form of treatment that was much easier to apply and that exhibited less toxicity [1]. However, with the standardized treatment protocol for glioblastoma, use of temozolomide only slightly improved survival outcome. Thus, treatments that include the combination of temozolomide with other drugs need to be tested [11–14]. The idea for this study originated from the hypothesis that a treatment that combined the existing effective protocol (ACNU-CDDP neoadjuvant chemotherapy followed by radiotherapy) with adjuvant use of the newer drug (temozolomide) would result in synergistic effects [5, 7]. The reason why temozolomide was not used with radiotherapy concurrently in both groups was that temozolomide was only approved in Korea for patients with uncontrolled malignant glioma at the time of study initiation. Temozolomide was later approved for newly diagnosed glioblastoma. Moreover, there was a concern about serial use of alkylating agents without a resting period in the treatment group, which might induce a higher risk of toxicity.

Synergy in the anticancer effects of nitrosourea and temozolomide has been demonstrated in a phase II trial for recurrent glioblastoma [13]. The idea of combining continuous infusion of a lipophilic drug such as nitrosourea with a hydrophilic agent such as CDDP for treatment of malignant glioma was developed as a potential improved anticancer strategy [4, 15]. In Korea and Japan, ACNU rather than BCNU and CCNU has been widely used for high-grade glioma treatment because of its easy availability [7]. Moreover, ACNU is better tolerated than BCNU, and the response rates to combination chemotherapy with ACNU-CDDP (41–59%) also appear to be better than those to BCNU-CDDP (23–42%) chemotherapy.[7, 16].

The poor response of glial tumors to chemotherapy might be due to the poor delivery of chemotherapeutic agents to the tumor, which is worsened by radiation-induced damage to the vascular supply to the tumor or hypoxia after radiation [7]. This mechanism may be responsible for the poor cytotoxic effects of chemotherapeutic agents on injured tumor cells during the period immediately after radiotherapy [17]. Moreover, radiation-induced changes to the integrity of the blood–brain barrier (BBB) make it difficult to evaluate the efficacy of chemotherapy given during or shortly after radiotherapy [5]. The strategy of neoadjuvant chemotherapy seems to have a beneficial rationale in that the enhanced delivery of a chemotherapeutic agent by these methods bypasses the aforementioned obstacles.

The median survival of 28.4 months and the 2-year survival rate of 50.9% in the treatment group are favorable survival results compared with historical outcomes [5, 7]. However, this favorable survival outcome failed to reach statistical significance relative to the control group. Enrollment of only half of the target population may account for this statistical outcome. Another reason for the lack of statistical significance of survival difference is that an imbalance in the introduction rate of secondary treatments at progression between the two groups may have distorted the survival outcome. Secondary treatment was performed in 21 (55.3%) patients in the control group but in only 10 (26.3%) in the treatment group. This difference suggests that patients in the treatment group were less tolerant of subsequent chemotherapy treatments.

However, the obstacle to the current study was serious hematological toxicity caused by ACNU-CDDP. The high risk of myelosuppression by nitrosourea is a well-known problem, and we have previously experienced such high toxicity profiles [5, 7, 16]. Moreover, many studies have reported that the hematological toxicities induced by nitrosourea are well tolerated by the majority of patients [4–7, 18]. In the past and despite its toxicity, use of this kind of chemotherapeutic agent was justified because it was the only drug for extending survival in this devastating disease. However, the introduction of temozolomide, an agent with comparable anticancer effects and much lower toxicities, has helped shift the way in which we evaluate cancer treatment outcomes. Specifically, increasing emphasis is placed on quality of life, which has created a new trend in cancer management that excludes anticancer agents with high toxicity. In our study, we observed a death that resulted from neutropenia and sepsis during the ACNU-CDDP phase of treatment. This was something we had never previously experienced. Therefore, this study was terminated because the serious hematological toxicity caused by the current protocol was unacceptable according to the modern trends of cancer management in patients with newly diagnosed glioblastoma.

Use of ACNU-CDDP for glioblastoma patients should be reserved as an alternative for those who are ineligible for the standard treatment protocol or as salvage treatment in recurrent cases. If future studies can define a subpopulation at low risk for ACNU-CDDP toxicity, this protocol could be re-introduced.

Conclusion

The high frequency of serious hematological toxicity with ACNU-CDDP neoadjuvant chemotherapy followed by

radiotherapy and adjuvant temozolomide limits its usage as primary treatment for glioblastoma.

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