Clinical Studies

Chemotherapy

Chemotherapy 2009;55:145–154
DOI: 10.1159/000214142

Received: August 19, 2008
Accepted after revision: January 20, 2009
Published online: April 22, 2009

Preradiation Chemotherapy with ACNU-CDDP in Patients with Newly Diagnosed Glioblastoma: A Retrospective Analysis

Jung Ho Han[a] Chul-Kee Park[b, e] Se-Hoon Lee[c, e] Chae-Yong Kim[a]
Dong-Wan Kim[c, e] Sun Ha Paek[b, e] Dong Gyu Kim[b] Dae Seog Heo[c, e]
Il Han Kim[d, e] Hee-Won Jung[b]

[a]Department of Neurosurgery, Seoul National University Bundang Hospital, Gyeonggi-do, Departments of [b]Neurosurgery, [c]Internal Medicine and [d]Radiation Oncology, Seoul National University Hospital, and [e]Seoul National University Hospital Cancer Research Institute, Seoul, Korea

Key Words
Glioblastoma · Preradiation chemotherapy · ACNU · Cisplatin · Survival

Abstract
Objective: We evaluated the benefit of preradiation chemotherapy with ACNU (nimustine) and CDDP (cisplatin) in patients with newly diagnosed glioblastoma by retrospective analysis. ***Methods:*** A total of 151 patients were newly confirmed to have glioblastoma between January 2000 and December 2004. All patients underwent surgical resection: 38 (25.2%) patients underwent complete resection, 73 (48.3%) underwent incomplete resection and 40 (26.5%) underwent biopsy. Preradiation chemotherapy using ACNU-CDDP was administered as an initial adjuvant therapy for 87 (57.6%) patients (ACNU-CDDP group), radiation therapy was performed in 31 (20.5%) patients (RT group) and the remaining 33 (21.9%) patients were treated with other regimens or refused to undergo further treatment. ***Results:*** The median survival time was 13 months (95% CI 11.29–14.71), and the overall survival rate was 54.0% at 1 year and 21.3% at 2 years. The differences in median survival time between the complete resection group and biopsy group and between the ACNU-CDDP group and RT group were significant (15.0 vs. 10 months, p = 0.028, and 16.0 vs. 12.0 months, p = 0.036, respectively) in the univariate analyses. Even in the multivariate analysis, preradiation chemotherapy using ACNU-CDDP had a significant effect on survival prolongation (HR = 0.628, p = 0.042). The usage of temozolomide for adjuvant or salvage therapy also had an independent and significantly positive effect on survival (HR = 0.511, p = 0.006). Grade 3 and 4 hematologic toxicities occurred in 28 (32.1%) patients in the ACNU-CDDP group, but there were no treatment-related deaths. ***Conclusion:*** Preradiation chemotherapy with ACNU-CDDP as an initial therapy for patients with newly diagnosed glioblastoma is feasible and should be assessed in a randomized phase III study.

Introduction

Glioblastoma is the most common primary brain tumor, comprising approximately 50% of all glial tumors [1]. It is one of the most notoriously difficult cancers to manage, and most patients with glioblastoma have a recurrence within 6–8 months after undergoing treatment with surgery and radiation [2]. The prognosis of glioblastoma remains poor as the overall survival of patients with

KARGER

Fax +41 61 306 12 34
E-Mail karger@karger.ch
www.karger.com

0009–3157/09/0553–0145$26.00/0

Accessible online at:
www.karger.com/che

Hee-Won Jung, MD, PhD
Department of Neurosurgery
Seoul National University College of Medicine
28 Yeongeon-dong, Jongno-gu, Seoul 110-744 (Korea)
Tel. + 82 2 2072 2355, Fax +82 2 744 8459, E-Mail hwnjung@snu.ac.kr

newly diagnosed glioblastoma is 14.6 months and the 2-year survival rate is 26.5%, despite advances in surgery, radiation therapy and chemotherapy [3, 4]. The role of chemotherapy in addition to radiation therapy in the treatment of malignant gliomas is less well defined [5]. However, the management of malignant glioma is entering a new era of hope thanks to the development of many novel chemotherapeutic agents and various multidisciplinary application protocols.

Since their introduction in the early 1970s, nitrosoureas have been used as a mainstay agent for the adjuvant treatment of malignant gliomas, and a large number of clinical trials have evaluated their role in glioblastoma and other malignant gliomas [6, 7]. Because of differences in their availability, ACNU (nimustine) has been used as a core agent for glioblastoma treatment in Korea and Japan, while BCNU (carmustine) or CCNU (lomustine) have been widely used in Western countries [8]. Several studies have demonstrated that the usage of nitrosourea as an adjuvant therapy to surgery and/or radiation leads to increased survival in patients with glioma [6, 7, 9, 10].

We previously reported the effectiveness and feasibility of preradiation chemotherapy with ACNU-CDDP in glioblastoma in the setting of a single-arm phase II clinical trial [7]. Based on this evidence, we have been managing newly diagnosed glioblastoma patients with preradiation chemotherapy with ACNU-CDDP in principle. Patients who were not in a condition to proceed with preradiation chemotherapy were treated with radiation therapy alone after surgery. Under these circumstances, we performed this retrospective study to evaluate the overall treatment outcome and efficacy of preradiation chemotherapy with ACNU-CDDP for patients with newly diagnosed glioblastoma.

Patients and Methods

Between January 2000 and December 2004, a total of 151 patients were confirmed to have newly diagnosed glioblastoma after histological evaluation at Seoul National University Hospital. All patient data were based on information contained in hospital charts and radiological studies and were collected in accordance with the case record form approved by the institutional review board. Clinical data, such as age, performance status [Karnofsky performance status (KPS) scales], survival, radiological characteristics, treatment modality and toxicity profiles were collected. Any data that were missing from the medical records because of incomplete follow-up were obtained through a telephone interview with the patient or, if the patient was deceased, with his/her relatives, after obtaining their permission.

Table 1. Postsurgery management of patients with newly diagnosed glioblastoma (January 2000 to December 2004, n =151)

	Initial management	Subsequent management
ACNU-CDDP	87 (57.6%)	
Radiation therapy		75 (49.7%)
Radiosurgery		1 (0.6%)
None		11 (7.3%)
Radiation therapy	31 (20.5%)	
None		19 (12.6%)
Temozolomide		7 (4.6%)
ACNU-CDDP		2 (1.3%)
Radiosurgery		2 (1.3%)
Radiation therapy (repeat)		1 (0.6%)
No further treatment or no data	26 (17.2%)	
Unspecified chemotherapy	3 (1.9%)	
Radiosurgery	2 (1.3%)	
PCV chemotherapy	1 (0.6%)	
Intracystic bleomycin	1 (0.6%)	

PCV = Procarbazine, lomustine and vincristine.

Eighty-nine (58.9%) of the patients were male and 62 (41.1%) of the patients were female. The mean age of the patients was 53 years (range 18–79). All patients underwent surgical resection or biopsy, and the diagnosis of glioblastoma was confirmed histologically in every case by neuropathologists based on the WHO criteria [11]. The extent of resection was classified as complete resection, incomplete resection or biopsy according to the evidence of residual enhancing lesions in magnetic resonance (MR) images performed within 48 h after surgery. There was no surgical mortality.

The details of the initial and subsequent adjuvant therapies after surgery are summarized in table 1. In principle, the treatment protocol for newly diagnosed glioblastoma patients in our institute during the aforementioned period conformed to that described in the previous report [7]. The preradiation chemotherapy with ACNU (40 mg/m^2/day) and CDDP (40 mg/m^2/day) by continuous intravenous infusion for 72 h was initiated at 2–3 weeks after surgery and was repeated after 6 weeks. A total of 2 cycles were administered unless the patient showed progressive disease, unacceptable toxicity or refused to undergo further treatment. Neurological examinations and MR imaging were performed before the second treatment cycle. Patients who showed radiological responses or were in a stable state without neurological deterioration were eligible for a second cycle of chemotherapy, while patients with tumor progression were referred for radiation therapy. In addition to tumor response, the treatment schedule was readjusted according to bone marrow function, renal function and hepatic function, as described previously [7]. Radiation therapy was initiated 6 weeks after the last cycle of chemotherapy with a total dose of 60 and 1.8 Gy per fraction with 5 fractions per week. The target volume included the postchemotherapy tumor volume

Table 2. Comparison of patient characteristics of ACNU-CDDP group and RT group

	ACNU-CDDP group (n = 87)	RT group (n = 31)
Mean age, years	45 ± 13	54 ± 13
Male	58 (66.7%)	14 (45.2%)
Central tumor location[1]	13 (14.9%)	5 (16.1%)
Extent of resection		
Complete resection	28 (32.2%)	5 (16.1%)
Incomplete resection	40 (46.0%)	22 (71.0%)
Biopsy	19 (21.8%)	4 (12.9%)
Functional status		
KPS 100	17 (19.5%)	2 (6.5%)
KPS 90	37 (42.5%)	8 (25.8%)
KPS 80	15 (17.2%)	5 (16.1%)
KPS 70	11 (12.6%)	5 (16.1%)
KPS 60	6 (7.0%)	5 (16.1%)
KPS 50	1 (1.2%)	6 (19.4%)
Temozolomide usage	20 (23.0%)	7 (22.6%)

[1] Central tumor location includes the corpus callosum, basal ganglia, thalamus and brainstem based on the tumor epicentre.

and surrounding edema with a margin of 3 cm, as defined by contrast enhanced MR images performed 6 weeks after the last cycle of chemotherapy. A total of 87 (57.6%) patients were enrolled in this protocol (ACNU-CDDP group).

The patients usually proceeded straight to radiation therapy if they were not eligible to undergo chemotherapy due to age older than 70 years and/or poor performance status or if there was any other reason to abandon chemotherapy. A total of 31 (20.5%) patients underwent radiation therapy after surgery without preradiation chemotherapy (RT group). The reasons for radiation therapy were as follows: poor functional status (12 patients), transfer to another hospital and/or old age (6 patients), patient or caregiver's choice (5 patients), other medical problems (4 patients), severe postoperative psychotic problems (3 patients) and pregnancy (1 patient). After radiation therapy, the patients were followed regularly with repeating MR images every 3 months unless they showed signs of deterioration. If the patient showed signs of disease progression other optional treatments, such as reoperation or temozolomide chemotherapy, were given.

Twenty-six of the remaining 33 (21.9%) patients refused further treatment, and 7 patients were treated with other regimens, such as PCV (procarbazine, lomustine, vincristine) chemotherapy, intracystic bleomycin injection and radiosurgery because they had already received radiation therapy or were transferred to another hospital that had different treatment protocols.

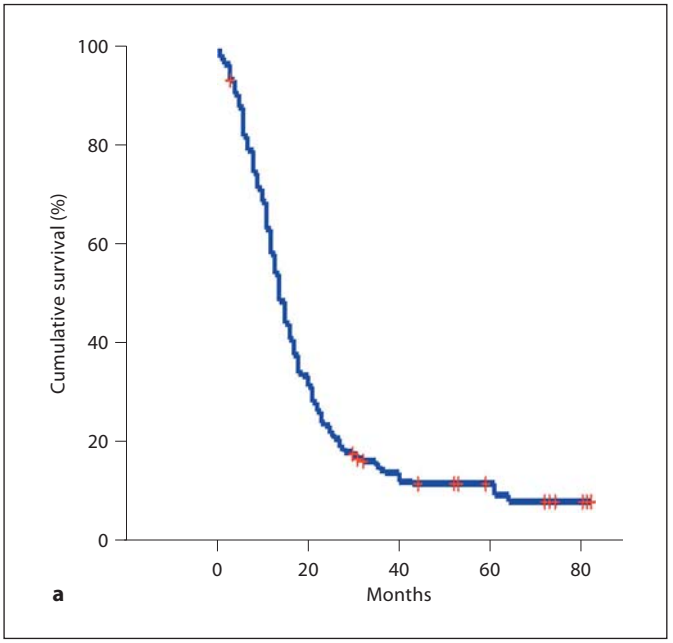
The overall survival and treatment-related toxicities were analyzed. Overall survival was defined as the time interval between the operation date and the date of death or the most recent evaluation. Toxicities were assessed using WHO common toxicity criteria version 3.0. The Kaplan-Meier method was used to estimate the overall survival distributions. The log-rank test (level of significance $\alpha = 0.05$) was used to test for differences in overall survival distributions with respect to the extent of resection and the initial adjuvant treatment modalities. We also performed statistical analyses for the subgroup of 118 patients comprising the ACNU-CDDP group and RT group in order to identify the efficacy of the treatment modality, with adjustment for possible confounding variables. The Cox proportional hazards model (level of significance $\alpha = 0.05$) was used to adjust for covariates. Confounding variables, such as the extent of resection, age, tumor location, functional status, and usage of temozolomide, were considered. A t test (level of significance $\alpha = 0.05$) was performed to compare the means between the 2 groups. All statistical analyses were performed using SPSS® v.12.0 (SPSS Inc., Chicago, Ill., USA).

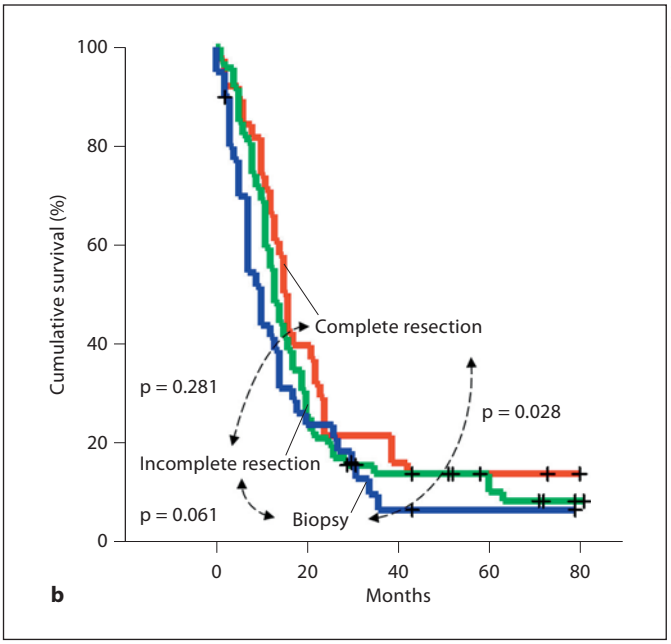
Results

General Information

Nine of the 151 patients had a history of grade 2 or 3 glioma diagnosed according to the WHO criteria [11] and 1 patient was diagnosed with radiation-induced glioblastoma after radiation therapy for medulloblastoma. The most frequent area of tumor location was the frontal lobe (32.5%) followed by the temporal lobe (29.8%), basal ganglia (15.9%), multilobe involvement (9.3%), parietal lobe (8.6%), infratentorial area (3.3%) and occipital lobe (0.6%). The typical radiological characteristics of gadolinium enhancement with or without necrosis were shown in 145 (96.0%) patients, while 5 (3.3%) patients did not show any enhancement. One patient (0.6%) presented primarily with intracerebral hemorrhage. Based on the radiological findings after surgery, 38 (25.2%) patients had complete resection, 73 (48.3%) patients had incomplete resection, and 40 (26.5%) patients had only biopsy.

The characteristics of the 118 patients in the ACNU-CDDP group and RT group are summarized in table 2. There were significant differences in the distribution of the mean age and mean functional status score between the 2 groups ($p < 0.001$ in both). However, the distribution of the extent of resection and the usage of temozolomide for adjuvant treatment or for recurrent disease were comparable between the 2 groups. Sixteen of the 27 patients who were treated with temozolomide received the treatment as an adjuvant to radiation therapy with or without preradiation chemotherapy, and 11 of these patients were treated with temozolomide as salvage therapy after recurrence at various time intervals after radiation therapy. In the ACNU-CDDP group, 8 (9.2%) patients (complete resection in 3 and incomplete resection in 5) underwent repeat surgical resection of recurrent or progressed tumor, and 1 (3.2%) patient with incomplete sur-





Color version available online

Fig. 1. a Kaplan-Meier estimates of overall survival of whole series (n = 151). The median survival time was 13 months (95% CI 11.29–14.71). The overall survival rate was 54.0% at 1 year, 21.3% at 2 years and 13.7% at 3 years. **b** Kaplan-Meier estimates of overall survival according to the extent of resection. Considering the extent of resection, the median survival time was 15.0 months (95% CI 12.99–17.01) in the complete resection group (n = 38), 13.0 months (95% CI 10.72–15.28) in the incomplete resection group (n = 73), and 10.0 months (95% CI 6.97–13.03) in the biopsy group (n = 40). There was a significant difference in survival time between the complete resection group and biopsy group (p = 0.028).

gical resection after initial surgery experienced reoperation in the RT group during the follow-up period after the initial management.

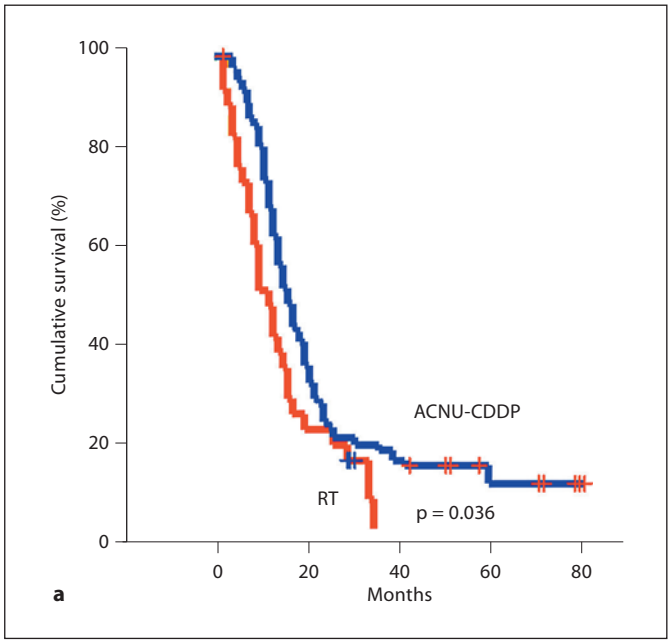
Overall Survival

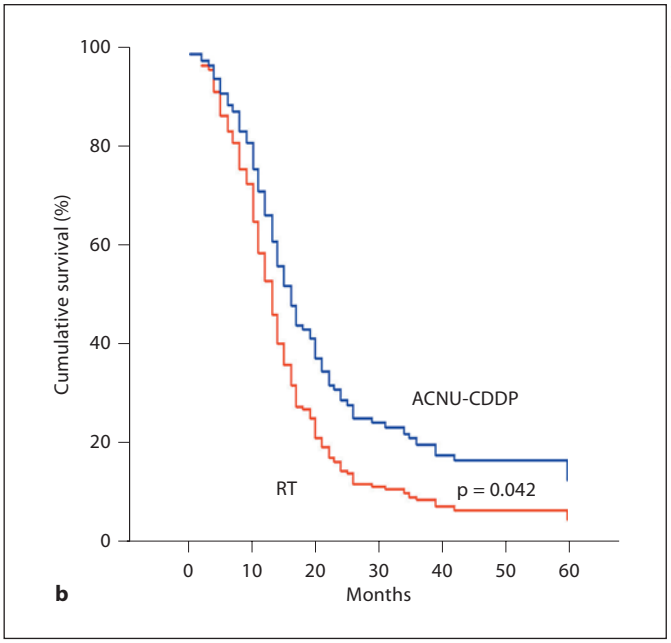
As of the cutoff date (April 10, 2007), 135 (89.4%) of the patients who were included in this series had died, 15 (9.9%) were alive and 1 (0.6%) was lost to follow-up. The median survival time was 13.0 months (95% CI 11.29–14.71), and the overall survival rate was 54.0% at 1 year, 21.3% at 2 years and 13.7% at 3 years (fig. 1a). The extent of resection had an influence on patient survival, regardless of whether or not the treatment was applied after surgery. The median survival time was 15.0 months (95% CI 12.99–17.01) in the complete resection group, 13.0 months (95% CI 10.72–15.28) in the incomplete resection group and 10.0 months (95% CI 6.97–13.03) in the biopsy group (fig. 1b). There was a significant difference in survival time between the complete resection group and biopsy group (p = 0.028); however, there were no differences in survival time between the complete and incomplete resection groups (p = 0.281). There was a difference in survival time between the incomplete resection group and biopsy group, but this difference was not statistically significant (p = 0.061).

The Efficacy of Preradiation Chemotherapy with ACNU-CDDP

The result of the prognostic value of variables related to survival in the 118 patients comprising the ACNU-CDDP group and RT group are shown in table 3. In the univariate analyses of the 118 patients in the ACNU-CDDP and RT groups, the usage of temozolomide and preradiation chemotherapy using ACNU-CDDP showed a significant survival benefit (p = 0.024 and p = 0.043, respectively). However, age, extent of resection, central tumor location and KPS ≥70 were not associated with overall survival. In the multivariate analysis, the usage of temozolomide, KPS ≥70 and preradiation chemotherapy were independently associated with overall survival (p = 0.006, p = 0.025 and p = 0.042, respectively).

The median survival time was 16.0 months (95% CI 13.52–18.48) in the ACNU-CDDP group and 12.0 months (95% CI 8.36–15.64) in the RT group (p = 0.036; fig. 2a).





Color version available online

Fig. 2. a Patients treated with preradiation chemotherapy of ACNU and cisplatin (n = 87, ACNU-CDDP group) showed significant survival benefit compared to patients treated with radiation therapy (n = 31, RT group). The median survival time was 16.0 months (95% CI 13.52–18.48) in the ACNU-CDDP group and 12.0 months (95% CI 8.36–15.64) in the RT group. Kaplan-Meier and log rank test (p = 0.036). **b** Survival estimates considering the usage of temozolomide, performance status of the patients, and tumor location shows significant difference between the ACNU-CDDP and RT groups using the Cox proportional hazard model (p = 0.042).

Table 3. Prognostic value of variables related to survival in the 118 patients comprising the ACNU-CDDP and RT groups

	Univariate analysis		Multivariate analysis		
	HR	p value	HR	p value	95% CI
Preradiation chemotherapy[1]	0.634	0.043*	0.628	0.042*	0.401–0.984
Temozolomide usage	0.583	0.024*	0.511	0.006*	0.316–0.826
Age (≥70 years)	1.216	0.671		ND	
KPS (≥70)	0.628	0.074	0.544	0.025*	0.320–0.925
Extent of removal[2]	1.174	0.467		ND	
Central tumor location[3]	1.564	0.095	1.699	0.050	1.001–2.885

ND = Not done. * Significant difference ($p < 0.05$).
[1] Preradiation chemotherapy using ACNU plus cisplatin.
[2] Biopsy or not.
[3] Central tumor location includes the corpus callosum, basal ganglia, thalamus and brainstem based on the tumor epicentre.

Table 4. Clinical information of long-term survivors (those who lived >3 years after diagnosis of glioblastoma)

Patient No.	Sex	Age years	Location	Resection	Primary management	Additional management	Survival months
1	M	30	frontal	biopsy	ACNU/CDDP (2) + RT	TMZ (6)	36
2	M	34	frontal	complete	ACNU/CDDP (2) + RT	TMZ (3), GKS	39
3	F	38	frontal	complete	ACNU/CDDP (2) + RT	TMZ (1), GKS	39
4	M	48	frontal	complete	ACNU/CDDP (2) + RT	GKS	42
5	F	59	temporal	incomplete	ACNU/CDDP (2) + RT	reop., PCV (2), reop.	43
6	M	30	parietal	complete	ACNU/CDDP (2) + RT		51
7	M	49	frontal	complete	ACNU/CDDP (2) + RT		52
8	M	46	temporal	complete	ACNU/CDDP (2) + RT	GKS, reop., TMZ (3)	58
9	F	45	frontal	incomplete	ACNU/CDDP (2) + RT	reop., ACNU/CDDP (2), TMZ (6), GKS	60
10	F	33	temporal	incomplete	ACNU/CDDP (2) + RT		71
11	M	36	frontal	incomplete	ACNU/CDDP (2) + RT		72
12	M	20	temporal	incomplete	ACNU/CDDP (2) + RT		79
13	F	57	frontal	complete	ACNU/CDDP (2) + RT	GKS	80
14	M	33	frontal	complete	ACNU/CDDP (2) + RT	TMZ (1), reop., TMZ (4)	81
15	F	38	frontal	incomplete	ACNU/CDDP (1) + RT		60
16	M	52	temporal	biopsy	ACNU/CDDP (1) + RT		79
17	M	56	thalamus	biopsy	ACNU/CDDP (1)		43
18	F	40	frontal	complete	RT		73
19	F	25	parietal	incomplete	intracystic blemoycin	Taxol (4), reop.	63

The number of cycles of each treatment are shown in parentheses. RT = Radiation therapy; TMZ = temozolomide; GKS = gamma knife surgery; PCV = procarbazine, lomustine and vincristine; reop. = reoperation.

The survival rate was 68.6% at 1 year and 24.4% at 2 years in the ACNU-CDDP group, and 48.4% at 1 year and 15.3% at 2 years in the RT group. This difference in overall survival between the ACNU-CDDP group and RT group remained significant, even after taking the major confounding variables of age, functional status and temozolomide usage into consideration (fig. 2b). Moreover, there were 19 (12.6%) patients who lived for more than 3 years, and the majority of them were from the ACNU-CDDP group (table 4).

Treatment-Related Toxicity

The details of the significant treatment-related toxicities observed in the ACNU-CDDP group and RT group are summarized in table 5. A total of 46 (52.9%) patients experienced hematologic toxicities during treatment in the ACNU-CDDP group. Grade 3 and 4 hematologic toxicities occurred in 18 (20.7%) and 8 (9.2%) patients during the chemotherapy phase, respectively, and during the radiation therapy phase in 1 patient (1.1%). On the other hand, only 4 (12.9%) patients in the RT group experienced hematologic toxicities and 2 of them were grade 3 and 4 toxicities.

As for the nonhematologic toxicities, 33 (37.9%) patients in the ACNU-CDDP group experienced dyspepsia, anorexia, nausea, vomiting, diarrhea, constipation, dysuria, alopecia and other infections. Twenty-three (25.3%) of these infections were of grade 3 or 4. In the RT group, 13 (41.9%) patients experienced nonhematologic toxicities such as anorexia, nausea, vomiting, myalgia, dyspepsia, alopecia and hepatotoxicity, but only 4 (12.9%) of them were grade 3.

Discussion

Over the past 4 decades, various strategies of clinical trials with various agents have been attempted in an effort to overcome the poor responses to chemotherapy for glioblastoma. The idea of combining the continuous infusion of a lipid-soluble drug with a water-soluble agent for malignant glioma was developed as a potential strategy [7, 10, 12, 13]. This tactic is based on the observation that even hydrophilic agents can cross the blood-brain barrier (BBB) when a sustained blood level is continuously maintained [14], and the anticancer effect is even

Table 5. Significant (grade 3 and 4) treatment-related toxicities

	ACNU-CDDP group (n = 87)				RT group (n = 31)	
	during ACNU-CDDP		during RT		during RT	
	grade III	grade IV	grade III	grade IV	grade III	grade IV
Hematological						
Pancytopenia	5	1				
Leukopenia	7	1				1
Neutropenia	2	3				
Anemia	2	1			1	
Thrombocytopenia	1	2		1		
Neutropenic fever	1		1			
Total (%)	18 (20.7%)	8 (9.2%)	1 (1.1%)	1 (1.1%)	1 (3.2%)	1 (3.2%)
Non-hematological						
Dyspepsia			1		1	
Anorexia			2			
Nausea/vomiting	8		3		2	
Diarrhea		1	1			
Constipation			1			
Dysuria			1			
Alopecia			4			
Myalgia					1	
Other infections	1	1				
Total (%)	9 (10.3%)	2 (2.3%)	13 (14.9%)		4 (12.9%)	

better if it is combined with a lipophilic agent [13]. Treatment with nitrosourea (lipophilic) and cisplatin (hydrophilic) is an example of this type of combination therapy. Moreover, there is no known cross-resistance between nitrosourea and cisplatin [15]. Grossman et al. [13] reported the promising result of a 95% tumor control rate in 52 patients with high-grade astrocytoma after 72 h of continuous intravenous infusion of BCNU and cisplatin prior to radiation therapy, and similar results were reported by Gilbert et al. [16]. Because of its availability and comparable effect to BCNU in the treatment of high-grade glioma reported in Japanese studies [8, 17–19], we used ACNU instead of BCNU in combination with cisplatin. Though ACNU was developed as a hydrophilic nitrosourea for the purpose of reducing the delayed myelosuppression of nitrosoureas, it can pass through the BBB at a rate of up to 30% [10, 20, 21], and it was better tolerated than BCNU [22]. In previous reports the response rates to combination chemotherapy with ACNU-CDDP have ranged from 41 to 59% [7, 10, 17] and they seem to be better than those of BCNU-CDDP chemotherapy, which range from 23 to 42% [13, 16, 23]. In addition, the treatment-related toxicities of the ACNU-CDDP regimen, especially the myelosuppression, seem to be better tolerated than those of BCNU-CDDP chemotherapy [7, 10, 13, 16, 17].

The poor response of glial tumors to chemotherapy might be due to the poor delivery of chemotherapeutic agents to the tumor, which might be more aggravated after radiation because of radiation-induced damage to the vascular supply to the tumor or hypoxia. This may decrease the cytotoxic effects of chemotherapy on dormant or injured tumor cells during the immediate period after radiation therapy [24, 25]. In addition, radiation-induced changes to the integrity of the BBB make it difficult to evaluate the efficacy of the chemotherapy given during or shortly after radiation therapy [7]. Pre-radiation chemotherapy has a beneficial rationale in that the enhanced delivery of a chemotherapeutic agent by these methods bypasses the aforementioned obstacles. However, when planning a treatment protocol for patients with newly diagnosed glioblastoma one should also remember that a delay in receiving radiotherapy after surgery is associated with reduced survival [26].

The authors have reported the promising result of preradiation chemotherapy with ACNU-CDDP in 30 patients with newly diagnosed glioblastoma, with a median overall survival of 14.9 months and a 41% tumor response, with tolerable toxicity [7]. As expected, the present study showed favorable results as the overall survival was 16.0 months and the survival rates at 1 and 2 years were 68.6 and 24.4%, respectively, in the patients treated with preradiation chemotherapy using ACNU-CDDP. Though there might be a bias in patient selection for preradiation chemotherapy, such as the younger mean age and the better functional status, the difference in the median survival time between the ACNU-CDDP and RT groups (16.0 and 12.0 months, respectively) was identified as significant in the mulitivariate analysis after correcting for the possible selection bias. We performed the multivariate analysis to avoid the difficulties of the univariate analyses such as the Kaplan-Meier method, the log rank test and a t test in comparing the variables between the groups that are not randomized, but there might still be a bias caused by the intention of the medical staff who decided the treatment modality. Considering that the calculated benefit of the preradiation chemotherapy with ACNU-CDDP had a relatively high p value (0.043), this regimen seems to be feasible and is probably not inferior to other published regimens.

Among 87 patients of the ACNU-CDDP group, 31 (35.6%) had received only 1 cycle of chemotherapy (1-cycle group) because of tumor progression (n = 13), adverse effect (n = 12) and so on. The median survival time was 12 (95% CI 8.36–15.64), 12 (95% CI 9.85–14.15) and 18 (95% CI 13.81–22.19) months in the RT group, the 1-cycle group, and the 2-cycle-or-more group, respectively. There were no obvious reasons for the lack of difference in survival time between the RT group and the 1-cycle group and for the difference in survival time between the 2-cycle-or-more group and the other groups. However, there seemed to be confounding variables such as the mean age (59 years for the RT group, 52 years for the 1-cycle-group and 46 years for the 2-cycle-or-more group) and the mean KPS (73.2 for the RT group, 84.2 for the 1-cycle-group and 85.7 for the 2-cycle-or-more group). One of the possible reasons is that there might be a subclass of glioblastoma which is resistant to a chemotherapy regimen using nitrosourea and cisplatin. However, more sophisticated studies may be necessary in order to confirm this hypothesis and our results. Furthermore, it is interesting to note that although we did not perform any further analyses, there were 19 (12.6% of a total of 151) patients with a survival time longer than 3 years. This seems to be one of the highest rates among those reported in the previous studies (range 1 to 17%) [27–31]. The majority of the long-term survivors (more than 3 years) in the present cohort underwent preradiation chemotherapy, which might reflect the efficacy of preradiation chemotherapy with ACNU plus cisplatin on the prolongation of the survival of patients with glioblastoma. However, it is also true that the majority of the long-term survivors were younger (median age 38 years) than the others, and they have a relatively good surgical result (47% of complete resection) and a high percentage (31%) of patients treated with temozolomide. Thus, these factors might affect the survival outcome as a confounding variable, and further studies are mandatory to identify the prognostic factors and the molecular or genetic characteristics of the tumor related with long-term survival.

One of the problems associated with the usage of ACNU-CDDP is the relatively high incidence of hematological toxicity. Hematological toxicities of grade 3 and 4 were observed in 29.9% of the 87 patients who received preradiation chemotherapy after surgery, which is similar to the incidence reported in a previous study [7]. However, these toxicities were tolerable and reversible, as mentioned above. These hematological toxicities are well-known complications of chemotherapy using nitrosourea as a core agent, and they are also known to be well-tolerated by the majority of patients [7, 10, 13, 16]. Thus, the relatively high incidence of hematological toxicities in this study seems to be a controllable problem in the management of glioblastoma patients. Nonetheless, one should also remember that the relatively young mean age of 45 years and good performance status of the ACNU-CDDP group in the present study is one of the possible reasons for tolerance of frequent hematological toxicities.

One of the most notable findings of the present study is that the usage of temozolomide had a significant effect on survival, although temozolomide had been used as an adjuvant or salvage therapy after recurrence at various time intervals following radiation therapy. The use of temozolomide might work as a confounder variable in the survival analysis of this study; however, its confounding effect may be minimal in analyzing the difference in survival between the patients in the ACNU-CDDP group and those in the RT group as the distribution of patients who were treated with temozolomide was minor in the present study. The use of temozolomide with radiation therapy has recently become a stan-

dard treatment for patients with glioblastoma, although its effect still falls short of our expectations [32, 33]. Nonetheless, its easy application and low toxicity make it a good candidate for combination therapy with other agents. The evaluation of the additive effect of ACNU-CDDP, radiation therapy and temozolomide will be another interesting study to perform. Based on the results of the present study, a randomized prospective phase III study is currently underway in an effort to acquire solid evidence of the benefit of preradiation chemotherapy with ACNU-CDDP and to evaluate the additive effect of temozolomide in patients with newly diagnosed glioblastoma.

Conclusion

Preradiation chemotherapy with ACNU-CDDP as an initial management is feasible for patients with newly diagnosed glioblastoma and treatment-related toxicities also seem to be tolerable. Further large-scale randomized prospective studies will provide conclusive evidence of its beneficial role in the treatment of glioblastoma.

Acknowledgment

This study was supported by a grant (study number 03-2007-026-0) from the Seoul National University Hospital Research Fund.

References

1 Mineo JF, Bordron A, Baroncini M, Ramirez C, Maurage CA, Blond S, Dam-Hieu P: Prognosis factors of survival time in patients with glioblastoma multiforme: a multivariate analysis of 340 patients. Acta Neurochir 2007;149:245–253.

2 Hau P, Baumgart U, Pfeifer K, Bock A, Jauch T, Dietrich J, Fabel K, Grauer O, Wismeth C, Klinkhammer-Schalke M, Allgauer M, Schuierer G, Koch H, Schlaier J, Ulrich W, Brawanski A, Bogdahn U, Steinbrecher A: Salvage therapy in patients with glioblastoma: is there any benefit? Cancer 2003;98:2678–2686.

3 Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E, Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med 2005;352:987–996.

4 Guensberg P, Wacheck V, Lucas T, Monia B, Pehamberger H, Eichler HG, Jansen B: Bcl-xL antisense oligonucleotides chemosensitize human glioblastoma cells. Chemotherapy 2002;48:189–195.

5 Stewart LA: Chemotherapy in adult high-grade glioma: a systematic review and meta-analysis of individual patient data from 12 randomised trials. Lancet 2002;359:1011–1018.

6 Walker MD, Green SB, Byar DP, Alexander E Jr, Batzdorf U, Brooks WH, Hunt WE, MacCarty CS, Mahaley MS Jr, Mealey J Jr, Owens G, Ransohoff J 2nd, Robertson JT, Shapiro WR, Smith KR Jr, Wilson CB, Strike TA: Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. N Engl J Med 1980;303:1323–1329.

7 Choi IS, Lee SH, Kim TY, Bang JS, Paek SH, Kim S, Kim IH, Heo DS, Bang YJ, Kim DG, Jung HW, Kim NK: Phase II study of chemotherapy with ACNU plus cisplatin followed by cranial irradiation in patients with newly diagnosed glioblastoma multiforme. J Neurooncol 2002;60:171–176.

8 Aoki T, Takahashi JA, Ueba T, Oya N, Hiraoka M, Matsui K, Fukui T, Nakashima Y, Ishikawa M, Hashimoto N: Phase II study of nimustine, carboplatin, vincristine, and interferon-beta with radiotherapy for glioblastoma multiforme: experience of the Kyoto Neuro-Oncology Group. J Neurosurg 2006;105:385–391.

9 Paoletti P, Butti G, Knerich R, Gaetani P, Assietti R: Chemotherapy for malignant gliomas of the brain: a review of ten-years experience. Acta Neurochir 1990;103:35–46.

10 Gwak HS, Youn SM, Kwon AH, Lee SH, Kim JH, Rhee CH: ACNU-cisplatin continuous infusion chemotherapy as salvage therapy for recurrent glioblastomas: phase II study. J Neurooncol 2005;75:173–180.

11 Kleihues P, Burger PC, Collins VP, Newcomb EW, Ohgaki H, Cavenee WK: Glioblastoma; in Kleihues P, Cavenee WK (eds): World Health Organization Classification of Tumours: Pathology and Genetics of Tumours of the Nervous System. Lyon, IARC Press, 2000.

12 Grossman SA, O'Neill A, Grunnet M, Mehta M, Pearlman JL, Wagner H, Gilbert M, Newton HB, Hellman R: Phase III study comparing three cycles of infusional carmustine and cisplatin followed by radiation therapy with radiation therapy and concurrent carmustine in patients with newly diagnosed supratentorial glioblastoma multiforme: Eastern Cooperative Oncology Group Trial 2394. J Clin Oncol 2003;21:1485–1491.

13 Grossman SA, Wharam M, Sheidler V, Kleinberg L, Zeltzman M, Yue N, Piantadosi S: Phase II study of continuous infusion carmustine and cisplatin followed by cranial irradiation in adults with newly diagnosed high-grade astrocytoma. J Clin Oncol 1997;15:2596–2603.

14 Norman D, Stevens EA, Wing SD, Levin V, Newton TH: Quantitative aspects of contrast enhancement in cranial computed tomography. Radiology 1978;129:683–688.

15 Gerosa MA, Rosenblum ML, Stevanoni G, Licata C, Della Corte V, Marcon C, Bricolo A, Tridente G: In vitro analysis of BCNU-sensitivity in human malignant gliomas. II. Cross-resistance studies with cisplatinum and nitrosoureas. Acta Neurol Scand 1986;73:66–70.

16 Gilbert M, O'Neill A, Grossman S, Grunnet M, Mehta M, Jubelirer S, Hellman R: A phase II study of preradiation chemotherapy followed by external beam radiotherapy for the treatment of patients with newly diagnosed glioblastoma multiforme: an Eastern Cooperative Oncology Group study (E2393). J Neurooncol 2000;47:145–152.

17 Iwadate Y, Namba H, Sueyoshi K: Intra-arterial ACNU and cisplatin chemotherapy for the treatment of glioblastoma multiforme. Neurol Med Chir 1995;35:598–603.

18 Kochii M, Kitamura I, Goto T, Nishi T, Takeshima H, Saito Y, Yamamoto K, Kimura T, Kino T, Tada K, Shiraishi S, Uemura S, Iwasaki T, Kuratsu J, Ushio Y: Randomized comparison of intra-arterial versus intravenous infusion of ACNU for newly diagnosed patients with glioblastoma. J Neurooncol 2000;49:63–70.

19 Takakura K, Abe H, Tanaka R, Kitamura K, Miwa T, Takeuchi K, Yamamoto S, Kageyama N, Handa H, Mogami H, et al: Effects of ACNU and radiotherapy on malignant glioma. J Neurosurg 1986;64:53–57.

20 Wakui A: Cancer chemotherapy with special reference to pharmacokinetics of nitrosoureas (in Japanese). Gan To Kagaku Ryoho 1982;9:1327–1338.
21 Shimizu K, Ushio Y, Hayakawa T, Mogami H: Combination chemotherapy with 1-(4-amino-2-methyl-5-pyrimidinyl)methyl-3-(2-chloroethyl)-3-nitrosourea hydrochloride and bleomycin in meningeal carcinomatosis in rats. Cancer Res 1980;40:1341–1343.
22 Weller M, Muller B, Koch R, Bamberg M, Krauseneck P: Neuro-Oncology Working Group 01 trial of nimustine plus teniposide versus nimustine plus cytarabine chemotherapy in addition to involved-field radiotherapy in the first-line treatment of malignant glioma. J Clin Oncol 2003;21:3276–3284.
23 Yung WK, Janus TJ, Maor M, Feun LG: Adjuvant chemotherapy with carmustine and cisplatin for patients with malignant gliomas. J Neurooncol 1992;12:131–135.
24 Volk PE DW: Radiation injury of the brain, Am J Neurol Radiol 1991;12:45–62.
25 Airley RE, Mobasheri A: Hypoxic regulation of glucose transport, anaerobic metabolism and angiogenesis in cancer: novel pathways and targets for anticancer therapeutics. Chemotherapy 2007;53:233–256.
26 Irwin C, Hunn M, Purdie G, Hamilton D: Delay in radiotherapy shortens survival in patients with high grade glioma. J Neurooncol 2007;85:339–343.
27 Krex D, Klink B, Hartmann C, von Deimling A, Pietsch T, Simon M, Sabel M, Steinbach JP, Heese O, Reifenberger G, Weller M, Schackert G: Long-term survival with glioblastoma multiforme. Brain 2007;130:2596–2606.
28 Senger D, Cairncross JG, Forsyth PA: Long-term survivors of glioblastoma: statistical aberration or important unrecognized molecular subtype? Cancer J 2003;9:214–221.
29 Davis FG, Freels S, Grutsch J, Barlas S, Brem S: Survival rates in patients with primary malignant brain tumors stratified by patient age and tumor histological type: an analysis based on Surveillance, Epidemiology, and End Results (SEER) data, 1973–1991. J Neurosurg 1998;88:1–10.
30 Salcman M, Scholtz H, Kaplan RS, Kulik S: Long-term survival in patients with malignant astrocytoma. Neurosurgery 1994;34:213–219; discussion 9–20.
31 Chandler KL, Prados MD, Malec M, Wilson CB: Long-term survival in patients with glioblastoma multiforme. Neurosurgery 1993;32:716–720; discussion 20.
32 van den Bent MJ, Hegi ME, Stupp R: Recent developments in the use of chemotherapy in brain tumours. Eur J Cancer 2006;42:582–588.
33 Reardon DA, Rich JN, Friedman HS, Bigner DD: Recent advances in the treatment of malignant astrocytoma. J Clin Oncol 2006;24:1253–1265.