

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

By the Neuro-Oncology Working Group of the German Cancer Society

Purpose: The role of chemotherapy in the primary treatment of malignant glioma remains controversial. The results from the German-Austrian Glioma trial (GAG, 1983 to 1988) demonstrated a survival benefit for chemotherapy using carmustine (BCNU) plus teniposide (VM26) over BCNU alone in addition to radiotherapy in patients with a Karnofsky performance score (KPS) more than 60. The Neuro-Oncology Working Group (NOA) of the German Cancer Society therefore compared the efficacy of nimustine (ACNU) plus VM26 and ACNU plus cytarabine (Ara-C) chemotherapy in addition to standard radiotherapy in patients with newly diagnosed malignant glioma.

Patients and Methods: From 1994 to 2000, 375 patients were randomly assigned to receive radiotherapy and cycles of ACNU 90 mg/m² intravenously (IV) on day 1 and VM26 60 mg/m² IV on days 1 to 3 (n = 183), or ACNU 90 mg/m² IV on day 1 and Ara-C 120 mg/m² IV on days 1 to 3 (n = 179), in 6-week intervals. Thirteen patients were not eligible after central neuropathology review. The remaining 362

patients had glioblastoma (n = 301) or anaplastic glioma (n = 61).

Results: Median survival and 2-year survival rates were 17.3 months and 25% for ACNU plus VM26, and 15.7 months and 29% for ACNU plus Ara-C in glioblastoma, and 60 months and 88% for ACNU plus VM26 and 62.5 months and 72% for ACNU plus Ara-C in anaplastic glioma. Multivariate analysis revealed no survival advantage for either arm or for subpopulations defined by histology, age, or KPS. Hematologic toxicity was more prominent in the ACNU plus Ara-C arm.

Conclusion: The median survival times and 2-year survival rates for patients with anaplastic glioma and glioblastoma achieved in the NOA-01 trial compare favorably with historical trials and with the Radiation Therapy Oncology Group database. The toxicity profile favors ACNU plus VM26 for further evaluation.

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THE STANDARD treatment for malignant gliomas includes surgical resection and postoperative involved-field radiotherapy. These therapeutic measures result in median survival times of approximately 1 year for patients with glioblastoma (World Health Organization [WHO] grade 4) and of 2 or more years for patients with anaplastic astrocytoma (WHO grade 3).¹⁻³ Several chemotherapy regimens have shown moderate efficacy in malignant gliomas that recur or progress after surgery and radiotherapy in phase II trials.^{4,5} The role of chemotherapy in addition to radiotherapy in the first-line treatment of malignant gliomas is less well defined.³ No phase III trial of the last two decades has further substantiated the notion that carmustine (BCNU) or any other chemotherapy regimen plus radiotherapy is more effective than radiotherapy alone.⁶ However, a reanalysis of two former phase III trials^{6,7} confirmed a small but significant advantage of radiotherapy plus BCNU chemotherapy compared with radiotherapy alone, independent of the major prognostic

factors.² In addition, a meta-analysis of 12 trials on the basis of individual patient data concluded that there is a significant prolongation of median survival of 2 months when chemotherapy is part of the first-line treatment of malignant glioma.³

The design of the Neuro-Oncology Working Group (NOA)-01 trial reported in this article was strongly influenced by the results of the earlier German-Austrian Glioma (GAG) trial that recruited 501 malignant glioma patients from 1983 to 1988. The GAG trial had compared whole-brain radiotherapy plus combination chemotherapy using BCNU and teniposide (VM26) with BCNU alone. The results from the GAG trial indicated an advantage of the combination chemotherapy that was significant for progression-free survival, but lacked significance for overall survival. A strong interaction between Karnofsky performance score (KPS) and type of chemotherapy became apparent on subgroup analysis and was confirmed in the multivariate analysis: patients with a KPS of 70 or more benefited from combination chemotherapy, whereas combination chemotherapy reduced survival in patients with a KPS below 70 (GAG Study Group, manuscript submitted for publication; Table 1). WHO grade and age showed no such interaction with the type of chemotherapy, although their strong influence on overall survival was confirmed.

The high rate of pulmonary toxicity of BCNU in the GAG trial provided the rationale for the NOA executive committee to substitute nimustine (ACNU) for BCNU in the subsequent NOA-01 trial. Unpublished pilot studies of ACNU alone had shown no relevant pulmonary toxicity in 51 patients with

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Table 1. Survival in the GAG Trial

	BCNU		BCNU + VM26	
	No. of Patients	Median Survival (months)	No. of Patients	Median Survival (months)
All	242	11.7	259	12.5
Grade				
III	43	25.3	47	23.9
IV	174	10.6	204	11.0
Age, years				
≤ 50	96	15.0	87	19.5
> 50	146	10.1	172	10.1
KPS				
< 70	67	10.7	74	8.4
≥ 70	175	12.0	185	15.3

Abbreviations: GAG, German-Austrian Glioma; BCNU, carmustine; VM26, teniposide; KPS, Karnofsky performance score.

recurrent and 49 patients with newly diagnosed malignant glioma who had their pulmonary function closely monitored. Furthermore, the superior activity of BCNU plus VM26 over BCNU alone for patients with a KPS of 70 or more in the GAG trial suggested that ACNU plus VM26 be evaluated as one arm of the ensuing NOA-01 trial. Cytarabine (Ara-C) was chosen as the experimental agent to be compared with VM26 as an adjunct to ACNU because of favorable single-center experience with Ara-C in 38 patients with recurrent and 50 patients with newly diagnosed malignant glioma. Finally, when the trial was initiated, whole-brain radiotherapy was no longer the standard type of radiotherapy for malignant glioma. Therefore, the NOA-01 trial compared ACNU plus VM26 and ACNU plus Ara-C in addition to involved-field radiotherapy in the first-line treatment of malignant glioma.

PATIENTS AND METHODS

Study Design

NOA-01 opened as a prospective trial in 1994. The study intended to randomly assign patients according to KPS to receive ACNU, no further chemotherapy after radiotherapy (KPS 50 to 60), ACNU plus VM26, or ACNU plus Ara-C (KPS 70 to 100). Eligible patients had WHO grade 3 or 4 glioma; were older than 15 but younger than 71 years of age; gave informed consent; and had WBC counts $\geq 4,000/\mu\text{L}$, platelets $\geq 100,000/\mu\text{L}$, creatinine ≤ 2 mg/dL, and bilirubin ≤ 3 mg/dL (inclusion criteria). Patients with a history of restrictive pulmonary disease, chronic heart failure, multiple sclerosis, or stroke were excluded. Patients were stratified according to biopsy or resection, as indicated by the neurosurgeons, and among the resected patients, according to study center.

The planned sample size was based on the results of the GAG trial. The study required 90 patients per low KPS arm to demonstrate a survival advantage of 1.55, and 210 patients per high KPS arm to demonstrate a survival advantage of 1.3 ($\alpha = 5\%$; $\beta = 20\%$).⁸ Survival time was the primary end point. The low KPS arms accrued 18 patients and were closed in 1997 because of poor patient accrual. An interim analysis for the high KPS arms revealed that a difference of 1.3 could not be expected even when recruitment was completed to enroll 210 patients per arm. Conversely, it was clear at the same interim analysis that the toxicity profile and the survival data were favorable in the NOA-01 trial compared with the GAG trial. These were secondary end points. The trial was therefore prematurely closed in 2000.

The high KPS arms recruited 375 patients from 1994 to 2000. Of these 375 patients, 13 were later excluded because central neuropathology review

performed at the German Brain Tumor Reference Center (Institute of Neuropathology, University Bonn, Bonn, Germany) did not confirm the diagnosis of anaplastic glioma (WHO grade 3) or glioblastoma (WHO grade 4). The remaining 362 patients represent the valid study group.

Of these patients, central neuropathology review was available for 331 patients. All tumors were classified according to the WHO classification and grading guidelines.⁹ Patients with only a local neuropathologic diagnosis had glioblastoma ($n = 25$), anaplastic astrocytoma ($n = 5$), and anaplastic oligodendroglioma ($n = 1$). The data summarized in Table 2 and used for multivariate analysis thus include 331 centrally confirmed diagnoses and 31 local diagnoses.

Surgery

The neurosurgeons were requested to indicate whether they had performed a biopsy or a resection. They were also asked to estimate whether they had removed 20% to 50%, 50% to 90%, or more than 90% of the tumor, or had performed a macroscopically complete resection. Early postoperative cranial computed tomography or magnetic resonance imaging was not mandatory.

Radiotherapy

All patients were scheduled to receive standard radiotherapy (60 Gy, 1.8- to 2-Gy fractions, five fractions per week) of the contrast-enhancing lesion (plus a 2-cm safety margin and the area of preoperative edema) starting between days 10 and 28 after surgery.

Chemotherapy

Chemotherapy was started between days 7 and 21 after surgery and was scheduled to be administered in four to five six-weekly cycles (ie, treatment for 3 days in 6-week intervals) for patients without residual tumor or in six-weekly cycles until tumor progression for patients with residual tumor. ACNU was started at 90 mg/m² administered at day 1. VM26 was started at 60 mg/m² and Ara-C was started at 120 mg/m²; both drugs were administered on days 1 to 3 of each cycle. Dose modifications were introduced according to early nadirs (before day 20, attributable to VM26 or Ara-C), late nadirs (after day 25, attributable to ACNU), or nadirs in between. ACNU was escalated to 100 mg/m² in the second cycle when the late WBC nadir was more than 2,500/ μL and the late platelet nadir was more than 75,000/ μL , and unless the early WBC nadir was less than 1,500/ μL and the early platelet nadir was less than 50,000/ μL . VM26 and Ara-C doses were escalated by 20% in the third cycle when the early WBC nadir was more than 2,500/ μL and the early platelet nadir was more than 75,000/ μL , and unless the late WBC nadir was less than 1,000/ μL and the late platelet nadir was less than 30,000/ μL . The dose of ACNU was reduced to 75% when the late WBC was less than 1,500/ μL or the late platelet nadir was less than 50,000/ μL . The doses of VM26 or Ara-C were reduced to 75% when the early WBC was less than 1,500/ μL or the early platelet nadir was less than 50,000/ μL . Treating physicians could act at their discretion to reduce either one or both drugs when the critical nadir was reached between days 20 and 25. Before the next cycle, WBC had to be more than 4,000/ μL and platelets had to be more than 100,000/ μL . Corticosteroids and anticonvulsants were administered at the discretion of the treating physicians. Patients were to be observed at 3-month intervals after the completion of study treatment. The experience in the GAG trial had shown that close monitoring of pulmonary function was a poor predictor of clinically relevant (and often fatal) pulmonary dysfunction in patients receiving BCNU. Therefore, no comparable assessment of pulmonary function was maintained in the NOA-01 trial. Instead, the gathering of clinical history information focused on pulmonary symptoms at each follow-up visit.

Statistical Analysis

The main end points, comparison of the distributions of survival time in both treatment arms of the NOA-01 study and comparison of the distributions of survival time in both studies (NOA-01 and GAG) with summarized treatments, were analyzed using Bonferroni adjusted log-rank tests. The

Table 2. Patient Characteristics in the NOA-01 Trial

Characteristic	ACNU + VM26		ACNU + Ara-C	
	No.	%	No.	%
No. of patients	183		179	
Females	75	41	57	32
Males	108	59	122	68
Age, all, years				
Median	50		51	
Range	17-73		22-72	
Age, all, years				
Mean	51		51	
SD	12		11	
Age, females, years				
Median	50		51	
Range	22-70		22-72	
Age, males, years				
Median	51		51	
Range	17-73		22-71	
Anaplastic glioma	29		32	
Astrocytoma	24		26	
Oligoastrocytoma	5		4	
Oligodendroglioma	0		2	
Glioblastoma	154		147	
Anaplastic glioma, age, years				
Median	46		48	
Range	22-61		29-69	
Glioblastoma, age, years				
Median	55		54	
Range	17-73		22-72	
History, weeks				
Mean	15.3		14.7	
SD	47.3		29.8	
Headaches	72	39	98	55
Increased intracranial pressure	25	14	31	17
Seizures	72	39	58	32
Biopsy	14	8	11	6
Resection	169	92	168	94
Macroscopic	74	40	69	39
> 90%	34	19	37	21
50%-90%	17	9	19	11
20%-50%	6	3	7	4
No data	41	22	36	20
KPS				
70	33	18	38	21
80	35	19	36	20
90	82	45	68	38
100	33	18	37	21
Spitzer index at study entry				
Patient				
Mean	6.3		6.4	
SD	3.6		3.6	
Physician				
Mean	6.7		6.6	
SD	3.3		3.3	
Spitzer index				
9-10				
Patient	65	36	62	35
Physician	70	38	63	35
7-8				
Patient	52	28	55	31
Physician	57	31	59	33
4-6				
Patient	24	13	23	13
Physician	24	13	24	13
< 4				
Patient	8	4	6	3
Physician	7	4	5	3
No data				
Patient	34	19	33	18
Physician	25	14	28	16

Abbreviations: NOA, Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; KPS, Karnofsky performance score; SD, standard deviation.

estimated survival times result from Kaplan-Meier analysis with asymmetric confidence limits using an equation described by Marubini and Valsecci.¹⁰ The median survival times and their confidence limits result from the SAS procedure LIFETEST (SAS/STAT User's Guide, 1999, Version 8, SAS Institute Inc, Cary, NC). Mantel-Haenszel estimates of the hazard ratios are supplemented. These hazard ratios approximate the inverse of the ratio of the median survival times as long as the survival times proved to be exponentially distributed with sufficient fit. The confidence limits for the hazard ratios result from a normal approximation using the hypergeometric distribution.

The influence of prognostic variables was explored by a multivariate analysis with the Cox proportional hazard model with stepwise selection of the potential prognostic factors. The resulting model with six variables should assume rough proportionality, although inhomogeneities were indicated by the residuals. Nevertheless, differences between both treatment arms were not apparent either in the univariate log-rank test or in the multivariate analysis. The procedures for the statistical analysis of the NOA-01 trial as delineated in the study protocol included a comparison of the NOA-01 data with the prior data of the GAG trial. This comparison was done once for all GAG patients with a KPS \geq 70 and once only for patients with a KPS \geq 70 who received combination chemotherapy, again using the above-mentioned univariate procedure. In addition, the study population was partitioned according to the groups generated by the recursive partitioning analysis (RPA) of the Radiation Therapy Oncology Group (RTOG)^{11,12} and the resulting hazard ratios were compared to those of the RTOG trials.

RESULTS

Patient Characteristics, Therapy, and Follow-Up

The patient characteristics for the valid study group are summarized in Table 2. No relevant differences between the two populations emerged. Glioblastoma was the most common histologic diagnosis. The majority of patients underwent open resection; however, as indicated, the extent of resection was estimated by the neurosurgeons, but was not assessed by mandatory early postoperative neuroimaging. The mean total doses of irradiation were 57.7 ± 6.9 Gy (range, 13 to 65 Gy) and 57.2 ± 8.8 Gy (range, 4 to 74 Gy), and the interval from surgery to first dose 30 ± 8.4 days (range, 12 to 73 days) and 32 ± 13.2 days (range, 18–145 days) in the ACNU plus VM26 (data from 154 patients) and ACNU plus Ara-C (data from 137 patients) arms, respectively. No relevant difference in the type of radiotherapy between the two treatment arms became apparent. Six patients in the ACNU plus VM26 arm (13, 16, 18, 29, 44, and 47 Gy) and eight patients in the ACNU plus Ara-C arm (4, 9, 16, 30, 35, 38, 42, and 47 Gy) received less than 50 Gy total dose, mostly because of early neurologic deterioration and tumor progression. The number of chemotherapy cycles and the total dose of ACNU administered in both arms were comparable (Table 3). Follow-up data as available are summarized in Table 4. Chemotherapy was halted in almost half of the patients because of tumor progression. Additional tumor-specific treatments at first recurrence or progression were documented in 114 patients (32%).

Toxicity

Hematologic toxicity was moderate, in general (Table 3). There were more relevant nadirs attributable to ACNU than to VM26 or Ara-C. In the ACNU plus Ara-C arm, there was a higher incidence of early and late grade 3 to 4 toxicity than in the ACNU plus VM26 arm. In the course of treatment, ACNU was

Table 3. Chemotherapy in the NOA-01 Trial: Doses and Hematologic Toxicity

	ACNU + VM26	ACNU + Ara-C
Interval from surgery to first day of chemotherapy, days		
Mean	22	23
SD	7.7	12.0
Range	8-61	8-132
Administered chemotherapy	480 cycles in 148 patients	473 cycles in 149 patients
Cycles		
Mean	3.29	3.15
SD	1.47	1.58
Dose per cycle, mg		
ACNU		
Mean	89.8	86.7
SD	7.7	7.8
VM26		
Mean	172	
SD	24.6	
Ara-C		
Mean		303
SD		60.7
Dose per patient, mg		
ACNU		
Mean	296	271
SD	136	135
VM26		
Mean	567	
SD	268	
Ara-C		
Mean		913
SD		441
Hematologic toxicity	223 cycles in 148 patients	234 cycles in 134 patients
WHO grade 3	42: 16 P, 31 L, 3 H	96: 50 P, 79 L, 4 H
WHO grade 4	12: 8 P, 5 L	59: 44 P, 25 L, 7 H
Early WHO grade 3 or 4 toxicity, P or L; < day 20	21	42
Late WHO grade 3 or 4 toxicity, P or L; > day 20	59	155
Dose modification		
Escalation \geq 10%		
ACNU	40%	20%
VM26	5%	
Ara-C		4%
Reduction		
ACNU	6%	6%
VM26	6%	
Ara-C		47%

NOTE. Determined only for cycles with complete follow-up including at least weekly blood tests.

Abbreviations: NOA, Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; SD, standard deviation; WHO, World Health Organization; P, platelets; L, leukocytes; H, hemoglobin.

reduced in 6% of the patients in each arm. VM26 was also reduced in 6% of the patients, whereas almost half of the patients (47%) required a dose reduction of Ara-C, indicating that the differential reduction strategy prevented an underdosage of ACNU in the Ara-C group. Conversely, the proposed individual dose escalation could be performed in 40% of the patients for ACNU and 5% of the patients for VM26 in the ACNU plus VM26 arm, and in 20% of the patients for ACNU and 4% of the

Table 4. Follow-Up and Cause of Death in the NOA-01 Trial

	ACNU + VM26 (No. of patients)	ACNU + Ara-C (No. of patients)
End of study treatment	123	124
Completed on schedule	18	18
Discontinued	105	106
Median time to end of study treatment, days	194	188
\pm SD	114	133
Reasons for discontinuation		
Major side effects	20	23
Contraindications	10	4
Patient wish	10	8
Tumor progression	60	60
Neurologic deterioration	22	29
Lost to follow-up	14	10
Further course after discontinuation of study treatment*		
Observation	58	54
Second surgery	13	26
Second radiotherapy	3	8
Second chemotherapy	33	31
Supportive care only	15	19
Causes of death		
Confirmed deaths	116	113
Tumor progression	103	104
Pulmonary embolism	5	4
Gastrointestinal bleeding		1
Sepsis or infection	5	3
Sepsis or infection (treatment related)	3	1
Unknown	3	1

Abbreviations: NOA, Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; SD, standard deviation.

*Some patients had more than one additional treatment.

patients for Ara-C in the ACNU plus Ara-C arm. Nonhematologic acute toxicity was comparable in both arms (Table 5). Despite the relative frequency of WHO grade 3 and 4 hematologic toxicity, hemorrhages or infections were uncommon, presumably because of the short duration of myelosuppression. As indicated in Table 4, three patients in the ACNU plus VM26 arm and one patient in the ACNU plus Ara-C arm died from septicemia during treatment-related myelosuppression.

Survival

Survival data broken down by treatment arm, histology, age, and KPS are listed in Table 6 and Figure 1. The median survival times were 60 months for anaplastic gliomas and 16.5 months for glioblastomas. At a median follow-up of 30 to 40 months, only one of 10 patients with oligodendroglioma or mixed anaplastic gliomas has died. Multivariate analysis revealed no difference in survival between the ACNU plus VM26 and ACNU plus Ara-C arms determined for the whole group, or separately for anaplastic glioma and glioblastoma, or any subgroup defined by age or KPS. Histology, age, and KPS were the most powerful predictors of survival (Table 7). A comparison of the NOA-01 and GAG trials showed a significant improvement in survival in the NOA-01 trial irrespective of whether the total NOA-01 population was compared with all GAG patients with a KPS \geq 70 (data

Table 5. Acute Nonhematologic Toxicity (day of application) and Other Side Effects in the NOA-01 Trial

Toxicity or Side Effect	Toxicity WHO Grade					No Data
	0	1	2	3	4	
Acute nonhematologic toxicity						
ACNU + VM26, 486 cycles						
Nausea or vomiting	388	54	20	9		15
Fever	460	3	7			16
Organic brain syndrome	469	2				15
Thrombosis	463	1	3	1	3	15
Allergy	469		1	1		15
Others	458	11				17
ACNU + Ara-C, 464 cycles						
Nausea or vomiting	349	55	26	7	2	25
Fever	424	6	9			25
Organic brain syndrome	432	4	3			25
Thrombosis	433	3	2	1		25
Allergy	439					25
Others	413	19	3	1		28
Side effects						
ACNU + VM26, 611 valid forms						
Pulmonary dysfunction	549	2	2			57
Hemorrhage (any)	546	2	3		1	59
Infection	514	16	7	10	5	59
Thrombosis	533	6	2	4	7	59
Nausea	473	53	15	7	3	60
Seizures	474	52	13	6	4	62
Others	487	29	10	9	4	72
ACNU + Ara-C, 616 valid forms						
Pulmonary dysfunction	535	2	3	2		73
Hemorrhage (any)	531	5	4	1		74
Infection	489	24	11	10	9	73
Thrombosis	523	8	3	3	5	74
Nausea	484	37	14	3	2	76
Seizures	473	43	17	6	4	73
Others	451	35	12	14	14	89

Abbreviations: NOA, Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; WHO, World Health Organization.

Table 6. Survival in the NOA-01 Trial

	No. of Patients	Median Survival (months)	1-Year Survival Rate (%)	2-Year Survival Rate (%)	3-Year Survival Rate (%)
All patients					
ACNU + VM26	183	19.1	70	37	25
ACNU + Ara-C	179	17.6	70	37	24
WHO grade III					
ACNU + VM26	28	60.0	93	88	64
ACNU + Ara-C	31	62.5	92	72	52
WHO grade IV					
ACNU + VM26	154	17.3	66	25	17
ACNU + Ara-C	148	15.7	65	29	17
Age ≤ 50 years					
ACNU + VM26	76	32.8	79	56	46
ACNU + Ara-C	83	21.2	79	47	31
Age > 50 years					
ACNU + VM26	107	15.9	63	21	9
ACNU + Ara-C	96	15.5	62	29	16
KPS 100					
ACNU + VM26	33	24.3	86	47	32
ACNU + Ara-C	37	18.5	65	40	24
KPS 90					
ACNU + VM26	82	19.3	70	38	25
ACNU + Ara-C	68	21.2	82	48	26
KPS 80					
ACNU + VM26	35	16.3	64	32	24
ACNU + Ara-C	36	17.3	68	31	27
KPS 70					
ACNU + VM26	33	14.2	57	23	15
ACNU + Ara-C	38	14.7	52	14	10
Resection	337	18.6	71	37	25
Biopsy	25	9.9	48	19	8

Abbreviations: NOA, Neuro-Oncology Working Group; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; KPS, Karnofsky performance score; WHO, World Health Organization.

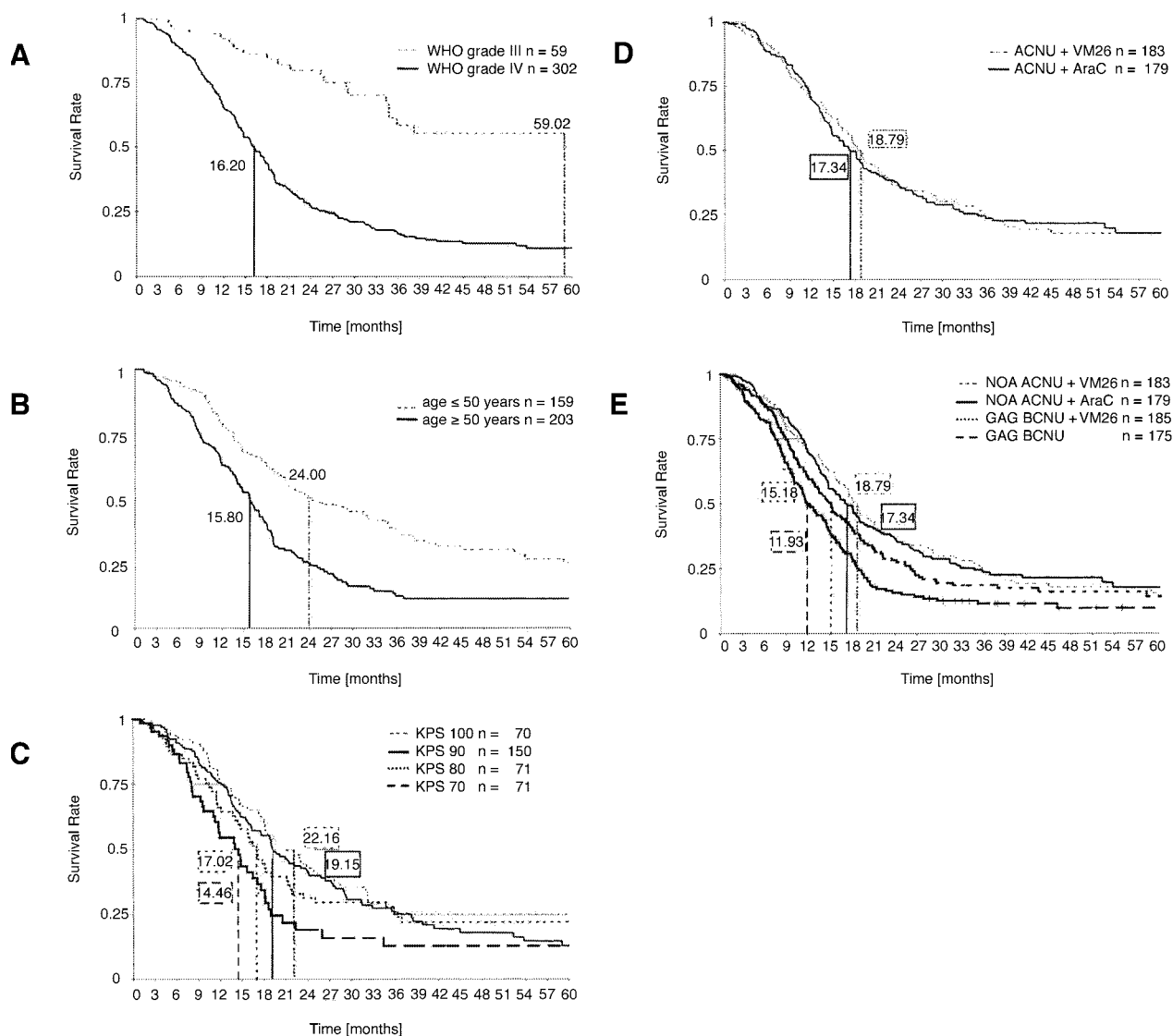


Fig 1. Survival in the Neuro-Oncology Working Group (NOA)-01 trial. (A) World Health Organization (WHO) grade 3 versus WHO grade 4 glioma; (B) effect of age (\leq 50 versus $>$ 50 years); (C) effect of Karnofsky performance score (KPS; 70, 80, 90, and 100 compared), (D) nimustine (ACNU) + teniposide (VM26) versus ACNU + cytarabine (Ara-C); and (E) comparison of the NOA-01 and German-Austrian Glioma (GAG) trials. BCNU, carmustine.

not shown) or only with those GAG patients with a KPS \geq 70 who received the combination chemotherapy of BCNU and VM26 (Table 8).

DISCUSSION

Major recent meta-analyses concluded that nitrosourea-based chemotherapy in addition to standard radiotherapy in the first-line treatment of malignant gliomas provides a small but significant and reproducible gain in median survival.¹⁻³ The NOA-01 trial reported here was initiated in the early 1990s when it was believed to be unethical (in Germany) to include a radiotherapy-only arm in a randomized phase III trial for malignant glioma patients with favorable prognostic factors (KPS \geq 70). This trial, therefore, does not provide additional data for the ongoing debate about whether chemotherapy should be considered standard in the first-line treatment of malignant glioma. However, it

would appear unlikely that the results of the NOA-01 trial could have been achieved with radiotherapy alone.

This prospective multicenter phase III trial reports better median survival times and 2-year survival rates for glioblastoma and anaplastic glioma (Table 6) than any other previous comparable phase III trial.¹⁻³ For instance, the 16.5 months of median survival for glioblastoma are superior to the 9 months of the Medical Research Council trial of procarbazine, lomustine, and vincristine in addition to radiotherapy¹³ or the 12 months of the phase III suicide-gene therapy trial.¹⁴ The central neuropathology review available for most patients with glioblastoma excludes the possibility that the encouraging results of the NOA-01 trial are confounded by the inclusion of too many nonglioblastoma histologies.

To exclude that the patients enrolled onto the NOA-01 trial represent a selected patient sample with favorable prognostic

Table 7. Prognostic Factors in the NOA-01 Trial

Variable	Univariate Nonparametric		Proportional Hazards Model			
	P (log-rank test)*	HR	HR Unifactorial	P Opt. Model	HR Opt. Model	HR 95% CI
Age groups, ref. < 30						
30-39	.109	0.50	0.54	.0020†	0.48	0.30 to 0.77
40-49	.873	0.95	0.95	.29‡		
50-59	.455	1.25	1.34	.29‡		
60 or older	.057	1.66	2.03	.0017†	1.58	1.19 to 2.11
Sex, ref. male						
Female	.155	0.83	0.82	.09‡		
WHO grade, ref. 3						
4	< .001	2.52	3.71	< .001†	3.34	2.13 to 5.24
Therapy, ref. ACNU + VM26						
ACNU + Ara-C	.889	1.02	1.02	.79‡		
Organic brain syndrome, ref. 0						
Mild	.470	1.11	1.10	.61‡		
Marked	.106	1.95	1.63	.60‡		
Neurologic disturbance, ref. none						
Mild	.102	1.25	1.24	.0335†	1.32	1.02 to 1.71
Moderate	.260	0.76	0.75	.19‡		
Severe	.620	0.68	0.62	.75‡		
Seizures						
Yes	.025	0.74	0.73	.50‡		
Increased intracranial pressure						
Yes	.076	1.40	1.35	.16‡		
Resection, ref. biopsy						
Yes	.015	0.47	0.56	.0131†	0.55	0.34 to 0.88
KPS, ref. 70						
80	.270	0.80	0.78	.82‡		
90	.022	0.63	0.66	.17‡		
100	.007	0.54	0.54	.0411†	0.76	0.58 to 0.99

Abbreviations: NOA, Neuro-Oncology Working Group; HR, hazard ratio; ACNU, nimustine; VM26, teniposide; Ara-C, cytarabine; KPS, Karnofsky performance score; WHO, World Health Organization; ref., reference; opt., optimized.

*Unadjusted.

†P value if eliminating from model.

‡P value if integrated into model.

factors, we analyzed the NOA-01 study population with the partition algorithm developed by the RTOG that has been validated with more than 7,000 patients enrolled onto RTOG trials.^{11,12} The RTOG RPA identifies six prognostic classes of malignant glioma patients on the basis of the following criteria: age, KPS, histology, mental status, duration of clinical symptoms preceding treatment, resection or biopsy, and radiation dose. Each individual NOA-01 patient was assigned the appropriate RTOG-RPA class. The estimates for the median survival

times and the 2-year survival rates were significantly improved in the NOA-01 trial in most RTOG-RPA classes (Table 9). The gain in survival in the NOA-01 trial appeared to be particularly marked in the poorer prognostic groups III to V. For instance, the confidence intervals of the median survival times for NOA-01 versus those of RTOG 90-06 or the RTOG database were (almost) nonoverlapping for RTOG-RPA classes III, IV, and V. Presumably because of low patient numbers, no advantage was achieved in the RTOG class I with the most favorable prognostic factors.

The substitution of ACNU for BCNU in the NOA-01 trial compared with the GAG trial was introduced because of the severe pulmonary toxicity encountered in the GAG trial, with an incidence of symptomatic restrictive lung disease of 12% per annum and 4% related deaths (GAG Study Group, manuscript submitted for publication). The comparison of the survival data in the NOA-01 and the GAG trials (Table 8; Fig 1E) illustrates that the change in nitrosourea from BCNU to ACNU did not compromise the overall outcome for the study population. Moreover, the pulmonary toxicity observed in the NOA-01 trial (Table 5) played almost no role compared with the incidence of pulmonary toxicity in the GAG trial mentioned above, although the

Table 8. Comparison of Survival in the NOA-01 and GAG Trials

Survival	NOA-01	GAG BCNU + VM26 KPS 70-100
No. of patients	362	185
Median survival, months	18.2	15.3
95% confidence interval	16.3 to 19.1	13.0 to 17.6
1-year survival rate, %	69.7	61.1
95% confidence interval	64.6 to 74.8	53.9 to 68.4
2-year survival rate, %	35.6	28.1
95% confidence interval	30.2 to 41.0	21.2 to 35.0
3-year survival rate, %	23.6	18.6
95% confidence interval	18.6 to 28.6	12.3 to 24.8

Abbreviations: NOA, Neuro-Oncology Working Group; GAG, German-Austrian Glioma; BCNU, carmustine; VM26, teniposide; KPS, Karnofsky performance score.

Table 9. Survival in the NOA-01 Trial in Different RTOG-RPA Classes

RTOG Classes	NOA-01			RTOG 90-06*			RTOG Database*		
	No. of Patients	Estimates	95% CI	No. of Patients	Estimates	95% CI	No. of Patients	Estimates	95% CI
I									
Median survival, months	28	59.2	29.0 to NA	84	NA		139	58.6	46.8 to 108.1
2-year survival, %		73.1	56.0 to 90.1		84	75.5 to 92.4		76	68.7 to 83.3
II									
Median survival, months	19	61.6	25.6 to NA†	13	10.3	7.5 to 15.7	34	37.4	26.2 to 45.9
2-year survival, %		75.6	54.8 to 96.5†		15	0 to 35.4		68	51.6 to 83.6
III									
Median survival, months	91	24.1	20.2 to 34.9†,‡	105	17.5	15.6 to 20.2	175	17.9	15.5 to 20.6
2-year survival, %		51.0	39.5 to 62.5†,‡		30	20.7 to 38.7		35	27.6 to 42.2
IV									
Median survival, months	117	15.8	12.5 to 18.24†,‡	240	11.5	10.8 to 12.7	457	11.1	10.4 to 11.9
2-year survival, %		22.8	14.3 to 31.3		17	12.2 to 22.1		15	12.0 to 18.0
V									
Median survival, months	99	14.5	13.1 to 16.56†,‡	150	7.4	6.2 to 9.1	395	8.9	8.3 to 9.5
2-year survival, %		20.1	11.5 to 28.6†,‡		8	3.3 to 12.2		6	4.0 to 8.0
VI									
Median survival, months	8	7.4	2.9 to 9.7†	23	2.7	1.7 to 4.5	263	4.6	4.3 to 5.3
2-year survival, %		16.7	0.0 to 46.5		0		4	1.8 to 6.2	

Abbreviations: NOA, Neuro-Oncology Working Group; RTOG-RPA, Radiation Therapy Oncology Group recursive partitioning analysis; NA, not assessable.

*Data from Scott et al.¹²

†NOA-01 superior to RTOG 90-06.

‡NOA-01 superior to RTOG database (median for RTOG below CI of NOA-01).

dose of ACNU was escalated in 30% of the patients (Table 3). These data indicate that ACNU may be equally effective but better tolerated than BCNU. Of note, given the lack of a difference between the VM26 and Ara-C arms, it is impossible to derive any conclusion regarding the contribution of VM26 or Ara-C, or their synergy with ACNU, to the encouraging results of the trial. This raises the important question of differences in efficacy and toxicity of ACNU plus VM26 versus ACNU alone.

The median survival for glioblastoma patients as observed in the NOA-01 trial is similar to the 16 months of the phase II trial of concomitant and adjuvant temozolomide in addition to radiotherapy for newly diagnosed glioblastoma.¹⁵ This is remarkable in that phase II trials commonly achieve better results

than phase III trials that evaluate the same regimen. Results from the European Organization for Research and Treatment of Cancer (EORTC) 26981/22981 phase III trial on the basis of this phase II temozolomide protocol will be available soon. If temozolomide plus radiotherapy is determined to be superior to radiotherapy alone in the EORTC 26981 trial, one may well consider a comparison of the chemotherapy arm of EORTC trial 26981/22981 with the ACNU plus VM26 arm of the NOA-01 trial in a future phase III trial. Such a trial would not only have to compare efficacy and side effects, but also (among other factors) quality of life and cost issues for radiochemotherapy regimens that may provide a modest advantage over radiotherapy alone.

APPENDIX

Administration responsibility: Neuro-Oncology Working Group (NOA) of the German Cancer Society. Writing committee: Michael Weller, Tübingen; Bettina Müller, Kreischa; Rainer Koch, Dresden; Michael Bamberg, Tübingen; Peter Krauseneck, Bamberg. Heads of clinical trial: Michael Bamberg, Tübingen; J. Bock, Düsseldorf. Clinical coordinators: Peter Krauseneck, Bamberg; Bettina Müller, Kreischa. Central pathology review: Otmar Wiestler, Bonn. Statistical analysis: Rainer Koch, Dresden; Bettina Müller, Kreischa. *The participating centers, in order of the number of patients entered (n), were as follows:* University of Tübingen, Departments of Neurology and Radiation Oncology, n = 105; Bamberg Clinic, Department of Neurology, n = 40; Bad Berka Clinic, n = 34; Ulm, Günzburg, and Augsburg Clinics, n = 30; University of Berlin Charité, Department of Radiation Oncology, n = 29; Ingolstadt Clinic, n = 25; Cologne-Merheim Clinic, n = 23; Trier Clinic, n = 17; University of Lübeck, n = 16; Erfurt Clinic, n = 13; Sande Clinic, n = 11; University of Giessen, n = 8; Bielefeld Clinic and University of Magdeburg, n = 6 each; Braunschweig Clinic and University of Essen, n = 4 each; Technical University Munich, n = 3; and University of Bochum, n = 1.

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