Vincristine in High-grade Glioma

BURCA AYDIN[1,2], MONALI PATIL[3], NEBIYOU BEKELE[4] and JOHANNES E.A. WOLFF[2,4]

[1]Department of Pediatric Oncology, Ankara Oncology Hospital, Ankara, Turkey;
Departments of [2]Pediatrics and [4]Biostatistics, The University of Texas
M.D. Anderson Cancer Center, Houston, TX 77030, U.S.A.;
[3]The University of Texas School of Public Health, Houston, TX 77225, U.S.A.

Abstract. *Aim: Numerous chemotherapeutics are used in the treatment of high-grade glioma (HGG). The purpose of this study was to evaluate the therapeutic value of vincristine (VCR) in the treatment of HGGs. Materials and Methods: A meta-analysis of HGG studies was performed to evaluate and compare the efficacy of chemotherapy drugs using observed and predicted median overall survival and survival gain as previously described. Results: Patient cohorts treated with VCR-containing-regimens had a significant survival gain advantage over cohorts treated with other chemotherapy drugs ($p<0.0001$). VCR was most effective in treating newly diagnosed adult ($p<0.0001$) and elderly ($p=0.0001$) patients. When VCR was combined with nimustine, carmustine, cytarabine or etoposide, the effect was antagonistic, but when VCR was combined with lomustine, procarbazine, cyclophosphamide, dacarbazine, hydroxyurea, or cisplatin it was synergistic. Conclusion: Results from this study suggest that VCR should be included in chemotherapy regimens for patients being treated for newly diagnosed or recurrent HGG.*

High-grade gliomas (HGGs) are a heterogeneous group of central nervous system tumors that generally have a poor prognosis. It may be due to the heterogeneity of HGGs that the value of many drugs remains unclear despite a large number of clinical studies (1-19). Chemotherapy, used in conjunction with surgery and/or radiotherapy (RT), has become an important part of multimodality treatment (1). Nitrosourea and platinum analogues have been reported to lengthen the survival time of patients with HGG (2-4); recently, temozolomide has become the standard of care in the treatment of glioblastoma, the most frequent form of HGG. Temozolomide has been studied extensively, and data supporting its efficacy have firmly established it as a standard treatment (1, 5, 6). Data supporting the efficacy of other drugs are less convincing, but this may be because other chemotherapy drugs have not been studied as extensively as temozolomide (2-4, 7-19).

Vincristine (VCR) has many clinical uses, including its application as a combination drug in many of the chemotherapy regimens used to treat HGG (7-11). The most frequently used drug combination is the PCV regimen, which consists of procarbazine (PRC), lomustine (CCNU), and VCR; this combination has been shown to be effective in treating HGG (12). However, the contribution of each individual agent is uncertain when a multi-drug regimen is used, and the success of the PCV regimen may be attributed to PRC and CCNU rather than VCR (7-11). The purpose of this study was to evaluate the therapeutic value of different chemotherapy drugs in order to determine the specific benefit of VCR in the treatment of HGGs.

A novel meta-analysis method that summarizes single cohorts, as opposed to controlled phase III studies, was developed and published recently (4). This method is particularly suited for cancers that have more phase II studies published than phase III data, such as HGG. In the present study, an expanded version of the previously published meta-analysis model was used to evaluate the efficacy of VCR in the treatment of patients with HGG (4, 13). Patient characteristics, such as age, tumor group, treatment details, and outcome measures, including median overall survival (mOS) times, from different clinical trials were analyzed. The meta-analysis compared the patient groups and their survival rates, taking covariates into account.

Materials and Methods

Literature search. This study is an extension of a previous meta-analysis, which tested a different hypothesis (the efficacy of VCR) but which used similar data (4, 13). The pre-existing database consisted of articles published between 1976 and April 2005. A new literature search from May 2005 to July 2009 was performed using the PubMed database; the search terms were glioma, glioblastoma, glioblastoma multiforme (GBM), anaplastic astrocytoma (AA), anaplastic oligodendroglioma (AO), and diffuse intrinsic pontine glioma (DIPG).

Correspondence to: Burca Aydin, Angora evleri Pusula sok no: 7 Beysukent, Ankara, Turkey. Tel: +90 3123360909/7046, Fax: +90 3124675238, e-mail: burcaaydin@yahoo.com

Key Words: High-grade glioma, HGG, treatment, vincristine, outcome.

Selection criteria. Abstracts were reviewed and every published English-language article that described a population of five or more patients with HGG was selected, including patient groups of mixed characteristics (*i.e.* from all ages or all known HGG types). Articles reporting laboratory only studies, abstracts for which no article was later published in a peer-reviewed journal and articles that were missing outcome descriptions were excluded. In cases of studies that duplicated patient cohorts, only the most recent publication was used for further analysis. If a given study consisted of more than one characteristic (*e.g.* randomized studies with two or more arms or studies consisting of more than one histopathologic group or age group with separate results for each group), the separate patient groups were entered into the database on separate lines to represent different cohorts. Studies which lacked outcome data were excluded.

Data reviewed. The latest version of the database consisted of 246 variables: reference information (8 items: author, year and publication information), patient cohort characteristics (36 items: age, gender, tumor grade, tumor location and previous treatments), treatment (106 items: surgery, radiation, chemotherapy and chemotherapy (CT)), outcome (66 items: treatment toxicity, details of response to treatment and survival rates) and data entry characteristics (30 items: data source, persons entering and reviewing data and survival gain calculations).

Outcome measures. mOS was chosen as being indicative of outcome. mOS was defined as 'observed outcome' (4). Missing mOS data were imputed with newly calculated values based on other outcome variables, such as 1-, 2- or 5-year overall survival, median progression-free survival, 6-month progression-free survival and response rates, as previously described.

Predicted outcomes for published patient cohorts were calculated as previously described (4). Predicted outcome presents an average overall survival for each cohort according to the given patient characteristics independent of treatment. Predicted outcome was calculated by multiple linear regression weighted by the square root of the number of patients and using known prognostic parameters (4). Parameters used for multiple linear regression analyses were percentage of tumors at the supratentorial location, percentage of male patients, percentage of brainstem gliomas, percentage of newly diagnosed patients, percentage of patients who received RT, radiation dose and percentage of patients with World Health Organisation (WHO) grade IV histology. These parameters were ranked according to their relationships, which were determined by Pearson's correlation and multiple regression analysis; the predicted mOS was therefore determined.

The difference between predicted outcome and observed outcome for each cohort was defined as 'survival gain'. Survival gain is a measure of the success for positive values and failure for negative values of any particular treatment in each cohort. This variable has been tested and validated in a previous report (4).

Statistical analysis. To determine if VCR extends survival, VCR effects on various clinical characteristics were analyzed. For both VCR-containing protocols and non-VCR treatment protocols, observed mOS and survival gain were calculated. The statistical significance of differences between the mean values of mOS and survival gain was tested with two-tailed independent sample *t*-tests. Since VCR was never used as a single agent, its effect had to be evaluated within combination therapies. In this more detailed analysis, the means of observed mOS and survival gain were compared using analysis of variance (ANOVA) for data describing VCR in combination with each additional drug in a cross-tabulated design. In this design, combination therapy was defined as having a negative effect if the survival gain of the combination was lower than the survival gain of each drug when used separately. An 'antagonistic effect' was defined as a negative effect with a p-value below 0.05 in a *t*-test. Similarly, if the survival gain of a two-drug regimen was equal to or higher than the survival gain of each drug individually, its effect was defined as 'additive'; if the *p*-value of an additive effect was <0.05, its effect was defined as 'synergistic'. All analyses were performed using SPSS v.12.0 (Statistical Package for Social Studies, SPSS Inc, San Francisco, CA, USA). *P*-values below 0.05 were considered statistically significant in all analyses.

Results

With the new PubMed search, 617 studies and 825 cohorts were considered for the database. Three of the cohorts were excluded because of duplication of the patient cohort, bringing the total number of patients to 41,488 in 822 cohorts from 614 studies for the new database (Figure 1).

Gender was available in 519 cohorts, consisting of 16,048 male (M) and 10,152 female patients (F); M:F ratio=1.6:1.0. The mean of median patient age was 45.3 (standard deviation [SD]: 15.5 years; range: 0-99 years). Most of the cohorts (526 cohorts, 64.0%) consisted of only adult patients. Seventy-eight cohorts (9.5%) consisted of only children, and 33 cohorts (4.0%) consisted of only elderly patients. One-hundred and eight cohorts (13.1%) contained mixed patient populations with respect to age. In the remaining 77 cohorts (9.4%), information regarding age was missing. The mean median Karnofsky score was 70 in 335 documented cohorts.

Histological data were documented for 40,783 patients; 28,746 patients (70.5%) from 287 cohorts had GBM, and 6,035 patients (14.8%) from 64 cohorts had AA. The remaining patients had either various other forms of HGG (3,068 patients, 7.5%) or unknown gliomas (2,934 patients, 7.2%). Tumors were located in the supratentorial region in 14,195 patients (34.8%), the infratentorial region in 1,138 patients (2.8%), the brainstem in 1,072 patients (2.6%), and the pons in 214 patients (0.5%). Localizations were not documented for the remaining patients (59.3%).

In 610 cohorts, multiple-agent chemotherapy regimens (303 cohorts) or single-agent chemotherapy regimens (307 cohorts) were documented. First-line treatment results for newly diagnosed patients were reported in 480 cohorts (58.4%). There were 309 patient cohorts (37.6%) with recurrent or progressive disease. Tumor response was evaluable in 13,276 patients and was classified as complete response in 400 patients (3.0%), partial response in 1,752 patients (13.2%), stable disease in 3,452 patients (26.0%), and progressive disease in 3,515 patients (26.5%). Tumor response was not specified for the remaining patients.

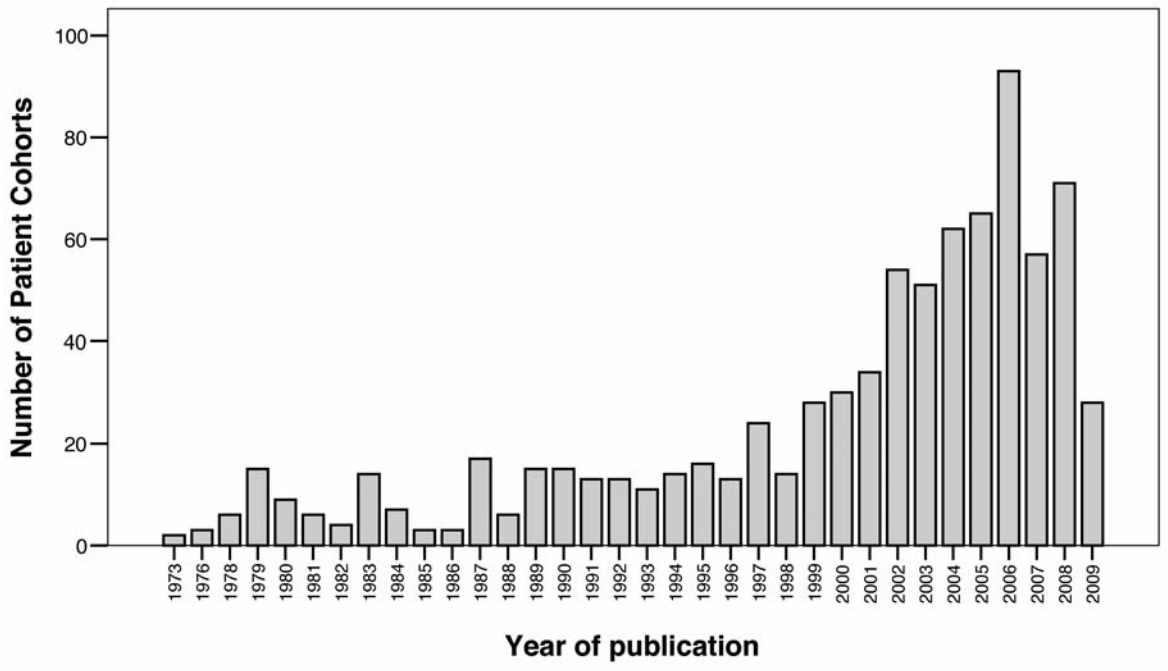

Figure 1. *Distribution of patient cohorts according to the year of study publication.*

mOS was reported in 604 cohorts; a summary of outcome variables are given in Table I. The mean of the mOS in these cohorts was 13.7 months (SD: 12.0 months). Missing mOS values were imputed by 1-year overall survival in 56 cohorts, median progression-free survival in 51 cohorts, 2- or 5-year overall survival in 12 cohorts, 6-month progression-free survival in 9 cohorts, and response to treatment in 75 cohorts. After imputation of missing mOS values, the mean of new mOS was 14.1 months (SD: 11.8 months). The mOS was found to be correlated with the percentage of tumors located in the supratentorial region (p=0.0508), percentage of tumors resected (p<0.0001), percentage of male patients (p=0.2), percentage of brainstem gliomas (p=0.009), median patient age (p=0.003), percentage of newly diagnosed patients (p<0.0001), percentage of children (p<0.0001), percentage of patients who received RT (p<0.0001), total radiation dose (p<0.0001), percentage of patients with WHO grade IV histology (p<0.0001) and median Karnofsky score (p=0.002). Male gender (p=0.1), supratentorial localization (p=0.4) and receiving RT (p=0.4) were found to have no effect on survival after weighted multiple linear regression analyses.

VCR-containing regimens were used to treat 3,707 patients from 97 cohorts, of which 2,920 were newly diagnosed patients and 787 were patients with recurrent or progressive disease. The number of children, adults and elderly patients treated with VCR-containing regimens was 536, 2700 and 78, respectively. Age groups were not documented in the remaining 393 patients. VCR was used in 1,530 patients with GBM and 1,043 patients with AA. Detailed characteristics of the cohorts treated with VCR-containing regimens and non-VCR regimens are given in Table II.

Table I. *Outcome of patients.*

	Mean of variable (months)	SD (months)	No. of cohorts
mOS	13.7	12.0	604
1-Year OS	48.7	21.6	373
mPFS	8.1	9.5	320
1-Year PFS	29.7	21.9	123
6-Month PFS	38.4	23.4	108
5-Year OS	21.4	18.0	91

SD: Standard deviation; mOS: median overall survival; OS: overall survival; mPFS: median progression-free survival: PFS: progression-free survival.

Mean mOS for cohorts treated with VCR-containing regimens was 22.9 months compared to only 12.6 months for cohorts treated with non-VCR regimens (p<0.0001) (Figure 2). Mean survival gain in cohorts treated with protocols that included VCR was 8 months longer than protocols that did not include VCR (p<0.0001). The efficacy of VCR held true in subgroup analyses. The mean mOS in newly diagnosed patient cohorts was 27.5 months for patients treated with VCR-containing regimens *vs*. 14.1 months without VCR (p<0.0001). In patients with recurrent or progressive disease,

Table II. *Characteristics of cohorts treated with VCR-containing regimens and cohorts treated with non-VCR regimens.*

Characteristics	VCR+		VCR–	
	N	%	N	%
Total	97		666	
Tumor status				
Newly diagnosed only	65	67.0	373	56.0
Recurrent or progressive	30	30.9	269	40.4
Mixture of new and recurrent	0	-	23	3.5
Unknown	2	6.7	1	0.4
Age				
Children only	33	34.4	41	6.2
Adults only	48	50.0	454	68.4
Elderly	4	4.2	23	3.5
Mixed ages	11	11.5	81	12.2
	Total=96		Total=599	
Histopathological subgroups				
GBM only	25	25.8	241	36.2
AA only	7	7.2	52	7.8
GBM/AA only	16	16.5	132	19.8
Mixed (all known HGG)	28	28.9	148	22.3
AO/AOA only	9	9.3	6	0.9
BSG only	5	5.2	18	2.7
Unknown	7	7.2	69	10.4

VCR+: Vincristine-containing regimen; VCR-: non-vincristine regimen; N: number of cohorts; %: percentage of cohorts; GBM: glioblastoma multiforme; AA: anaplastic astrocytoma; HGG: high-grade glioma; AO: anaplastic oligodendroglioma; AOA: anaplastic oligoastrocytoma; BSG: brainstem glioma.

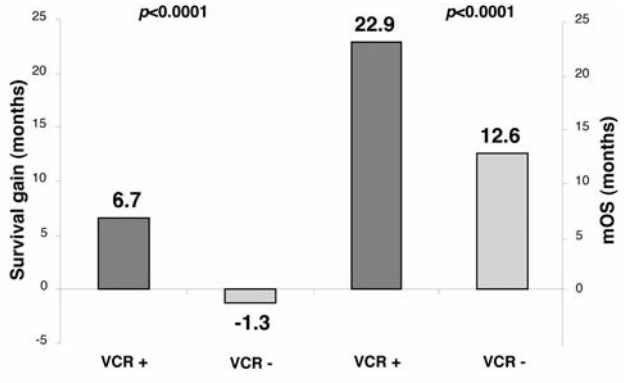

Figure 2. *Means of survival gain and median overall survival (mOS) of cohorts treated with VCR-containing regimens (VCR+) and cohorts treated without VCR (VCR–).*

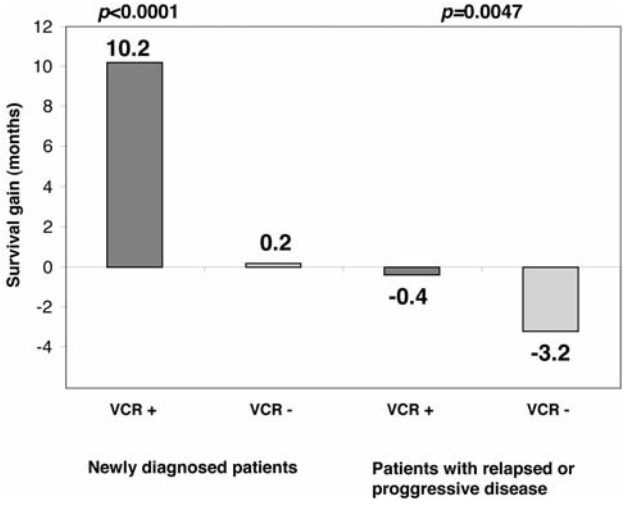

Figure 3. *Means of survival gains in newly diagnosed patients and patients with recurrent or progressive disease.*

the mOS for patients treated with VCR-containing regimens was 13.7 months compared to only 9.9 months without VCR ($p<0.0001$). Equivalent results were found for the survival gain calculation (Figure 3). Excluding children and elderly patients from the analysis did not change the outcome. A significant survival benefit was found for VCR-containing regimens (mean mOS with VCR 26.4 months *vs*. 12.3 months without). Similar results were found when restricting the analysis to elderly patients (12.9 months with VCR *vs*. 4.6 months without VCR; $p=0.001$; Figure 4). Among all cohorts, 1,610 children with HGG were treated, most of them within adult series. Considering only children, VCR was used to treat 33 cohorts consisting of 536 patients. In 9 of these cohorts, 164 children (30.6%) were treated with the 8-in-1 protocol. Mean survival gain and observed mOS of children treated with this regimen were 1.5 months and 19.0 months, respectively. Survival gain and mOS of all children were 0.1 month and 17.1 months, respectively. The drugs most frequently combined with VCR in the treatment of children were CCNU in 20 cohorts, cisplatin in 15 cohorts, PRC in 14 cohorts, cytarabine in 10 cohorts, dacarbazine (DTIC) and hydroxyurea in 9 cohorts each, etoposide in 8 cohorts and cyclophosphamide in 6 cohorts.

Among the histopathological subgroups, AO and anaplastic oligoastrocytoma had the most significant benefit from VCR (56.5 months with VCR *vs*. 28.5 months without VCR). mOS was also higher in AA and GBM (22.7 months with VCR *vs*. 18.8 months without VCR in AA; 12.8 months with VCR *vs*. 10.9 months without VCR in GBM). No significant effect of VCR could be detected in patients with brainstem glioma.

VCR was always used in combination with other drugs in multi-drug chemotherapy regimens. Unfortunately, no cohorts with VCR monotherapy were found to match the eligibility criteria for this analysis. Therefore, for each drug that VCR was combined with, the effects of the drug combination were compared with the effects of the other drug without VCR. CCNU and PRC were the drugs most frequently combined

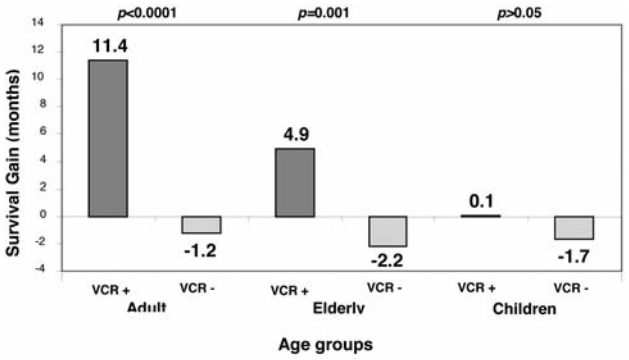

Figure 4. *Means of survival gains in children, adults and elderly patient cohorts that were treated with VCR (VCR+) and without VCR (VCR–).*

with VCR in 45 cohorts and 48 cohorts, respectively. Mean survival gains of VCR combined with other drugs are given in Table III. For several drugs, the data do not show any benefit of combining them with VCR. For example, the mean survival gain of the 9 cohorts treated with VCR in combination with etoposide was only 0.2 months. But in 38 cohorts where etoposide was used without VCR, mean survival gain was 1.9 months. Similarly, mean survival gain in the 88 cohorts where VCR was used without etoposide was 7.4 months (Figure 5A). This suggested that it may be better to give VCR and etoposide separately. Similar drug interactions were found for carmustine (BCNU) and VCR combinations. Although overall effect was poor for BCNU, mean survival gain was even poorer when it was combined with VCR (Figure 5B). Further antagonistic effects were observed when carboplatin, cyclophosphamide, temozolomide, cisplatin, hydroxyurea, cytarabine or nimustine (ACNU) were added to VCR.

On the contrary, several other drug combinations appeared beneficial. Figure 6 shows the results of VCR combined with CCNU (Figure 6A) and VCR combined with PRC (Figure 6B). Although survival gain for each individual drug was poor, the combination effect was synergistic. VCR had a synergistic effect when it was added to CCNU, PRC, DTIC, cyclophosphamide, hydroxyurea and cisplatin; VCR had an antagonistic effect when it was added to cytarabine, etoposide, BCNU and ACNU (Figure 7). Similarly, synergistic effects were observed when CCNU, DTIC and PRC were added to VCR.

Table III. *mOS and survival gain of cohorts comparing other drugs which were used with VCR and without VCR.*

	VCR+		VCR–		
	SG	n	SG	n	*p*-Value
BCNU+	–5.9	6	–0.8	92	
BCNU–	–5.9	6	–0.9	92	
					p<0.0001
CCNU+	10.1	68	–2.1	20	
CCNU–	–1.2	29	–1.2	633	
					p<0.0001
ACNU+	3.2	8	8.9	21	
ACNU–	7.0	89	–1.5	638	
					p<0.0001
Procarbazine+	9.7	71	–4.4	15	
Procarbazine–	–1.3	26	–1.2	650	
					p<0.0001
Cytarabine+	2.4	12	15.2	5	
Cytarabine–	7.3	85	–1.4	660	
					p<0.0001
DTIC+	2.5	11	–3.3	6	
DTIC–	7.3	86	–1.2	660	
					p<0.0001
Temozolomide+	0.3	2	0.3	111	
Temozolomide–	6.9	95	–1.5	543	
					p<0.0001
Cyclophosphamide+	1.5	7	–6.5	9	
Cyclophosphamide-	7.1	90	–1.2	656	
					p<0.0001
Hydroxyurea+	3.9	17	–3.8	10	
Hydroxyurea–	7.3	80	–1.2	654	
					p<0.0001
Cisplatin+	2.6	19	0.2	44	
Cisplatin–	7.7	78	–1.4	620	
					p<0.0001
Carboplatin+	–0.5	8	0.2	27	
Carboplatin–	7.6	88	–1.3	632	
					p<0.0001
Etoposide+	0.2	9	1.9	37	
Etoposide–	7.4	88	–1.4	622	
					p<0.0001

SG: Survival gain; n number of cohorts; VCR: vincristine; BCNU: carmustine; CCNU: lomustine; ACNU: nimustine; DTIC: dacarbazine; +: presence of drug in treatment regimen; –: absence of drug in treatment regimen.

Discussion

In a meta-analysis summarizing 617 publications, it was found that VCR has a positive impact on the outcome of HGG. Patient cohorts treated with VCR as a component of the treatment regimen had clearly better outcomes than those on regimens without VCR. VCR added an average of 10 months to the reported mOS. In newly diagnosed patients, the effect of VCR on survival was even higher. There were no data on using VCR alone, and in combination regimens it was not easy to distinguish the contribution of each constituent drug to the effect. In order to analyze individual drug effects the effects of drug combinations with each other were compared and then these combinations were scrutinized (Figure 7, Table III). In this analysis, VCR had strong non-linear interactions either synergistic (combined treatment effect was bigger than the individual effects of each constituent drug) or antagonistic (combined treatment effect was smaller than the individual effects of each constituent

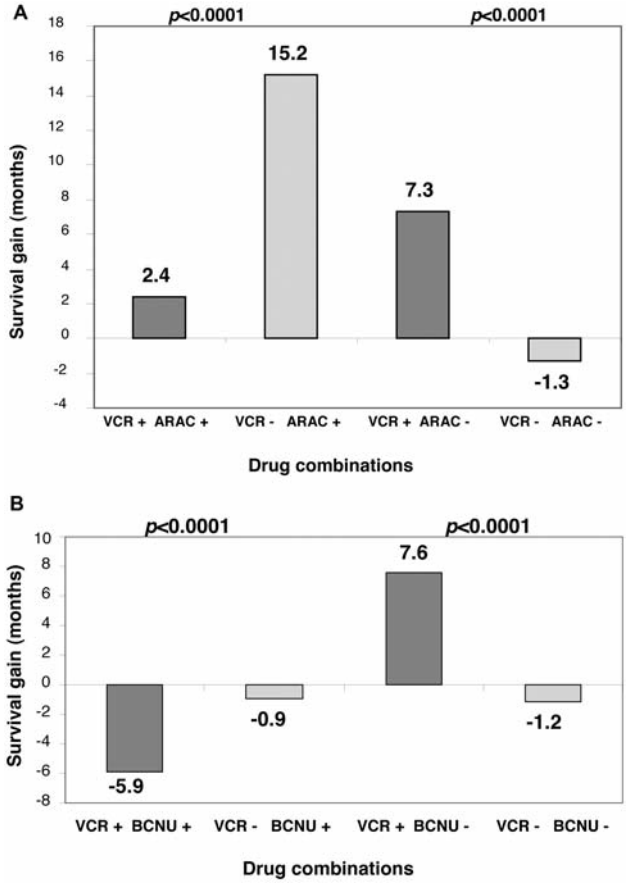

Figure 5. *Antagonistic drug combinations with (+) and without (–) drugs.*

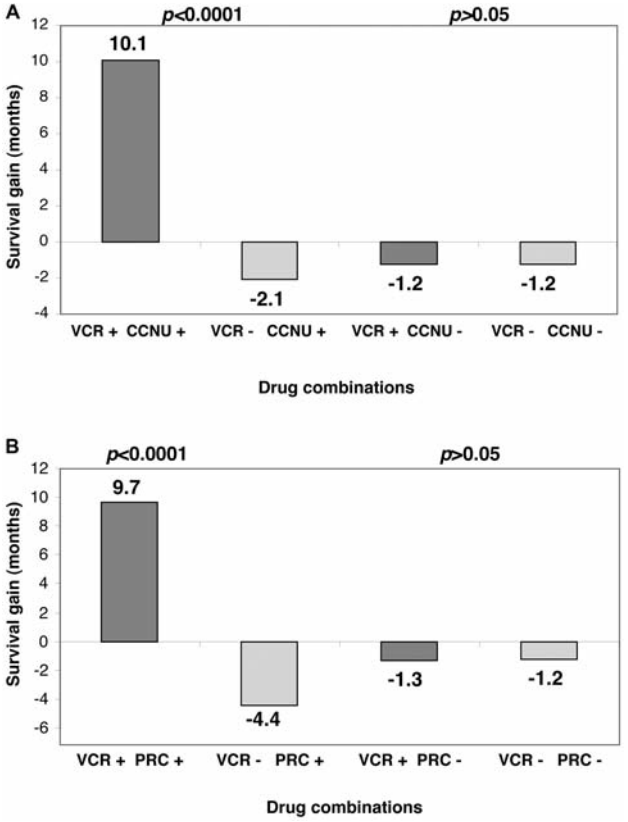

Figure 6. *Synergistic drug combinations with (+) and without (–) drugs.*

drugs) with most other drugs. VCR had a synergistic effect when combined with CCNU, PRC, DTIC, cyclophosphamide, hydroxyurea and cisplatin, while an antagonistic effect was observed when VCR was combined with ACNU, BCNU, cytarabine and etoposide. The strongest interactions occurred with the CCNU-VCR and PRC-VCR combinations. The addition of VCR to a PRC regimen added 9.7 months to mOS, which confirms the results of a recent meta-analysis of PRC (3). Goerne *et al*. (3) reviewed studies consisting of PRC and suggested that PRC should not be used as a single agent for the treatment of HGG. The CCNU and VCR combination showed a similar result. The outcome of cohorts consisting of CCNU without VCR was not better than without CCNU, but adding VCR improved survival. The well-known combination of CCNU, PRC and VCR seemed to be very effective, suggesting that VCR enhanced the antitumor effects of the other two drugs (14-18). The concern that VCR does not cross the blood-brain barrier (19, 20) did not appear to have a correlation in clinical data for HGG (21).

The method of meta-analysis of phase II studies applied in this study is novel, and therefore worthy of consideration. This study was a treatment arm summarizing analysis that compiled information from the literature. The challenge was to compare different outcome parameters of different styles of studies. The primary endpoints in phase II and phase III studies are response rate and survival, which are difficult to compare in a pool of cohorts. The input of missing survival variables using other outcome parameters and survival gain analysis made it possible to combine and compare the cohorts. The mathematical model used in this study to normalize the outcome utilized the information provided in the published description of the patient populations. Refinement of this model may improve the method.

The interactive effects of VCR seemed to be drug specific. VCR enhanced the effect of CCNU but not other nitrosoureas. The overall effect was antagonistic when VCR was combined with ACNU and BCNU. ACNU was found to be an effective drug without VCR and added 8.9 months to survival. BCNU, unlike ACNU, showed no benefit for HGG with or without VCR. This finding confirms previous reports (4, 12, 22). Moreover, BCNU seemed to diminish the efficacy of VCR. Although some studies reported better results with combinations of BCNU, VCR and PRC, these results may come from the synergistic interaction of VCR and PRC (14, 23).

Have patient on ► / Add drug ▼	BCNU	CCNU	ACNU	DTIC	TMZ	PRC	Cyc	HU	Cisp	Carb	ARAC	VP16	Tenip	VCR
BCNU		3 A	0	0	4 -	8 A	1 -	5 -	17 0	2 -	0	4 -	2 -	6 A
CCNU	3 A		0	11 +	4 +	58 S	2 +	17 +	13 -	3 +	12 -	2 +	4 -	68 S
ACNU	0	0		0	0	6 A	0	0	2 +	1 -	2 S	2 +	3 +	8 A
DTIC	0	11 -	0		0	11 A	0	11 +	11 +	0	11 -	0	0	11 S
TMZ	4 -	4 -	0	0		2 A	1 +	0	3 -	1 +	0	2 -	0	1 -
PRC	8 A	58 S	6 A	11 S	2 A		1 +	18 +	11 +	2 +	11 -	0	2 -	71 S
Cyc	1 -	2 +	0	0	1 +	1 -		0	6 +	2 -	0	8 -	0	7 A
HU	5 0	17 -	0	11 +	0	18 -	0		13 +	0	13 -	0	1 -	17 A
Cisp	17 +	13 -	2 +	11 +	3 -	11 -	6 +	13 0		0	14 -	18 +	0	19 A
Carb	2 -	3 -	1 0	0	1 +	2 +	2 +	0	0		1 -	12 +	1 -	8 A
ARAC	0	12 -	2 +	11 +	0	11 -	0	13 0	14 S	1 0		2 +	0	12 A
VP16	4 +	2 +	2 +	0	2 -	0	8 +	0	18 +	12 +	2 +		0	9 A
Tenip	2 0	4 -	3 +	0	0	2 -	0	1 -	0	1 0	0	0		0
VCR	6 A	68 S	8 A	11 S	1 0	71 S	7 S	17 S	19 S	8 0	12 A	9 A	0	

Codes: Antagonistic ■ Negative effect not significant ▒ Synergistic ▓ Positive effect not significant ▒

Figure 7. *Interactions (synergistic and antagonistic) of drug combinations according to survival gain. Numbers in the upper line of each row represent the number of cohorts that used the two drugs in combination. '0' in the lower line of the row represents 'no observed effect' for that drug combination. BCNU: Carmustine; CCNU: lomustine; ACNU: nimustine; DTIC: dacarbazine; TMZ: temozolomide; PRC: procarbazine; Cyc: cyclophosphamide; HU: hydroxyurea; Cisp cisplatin; Carb carboplatin; ARAC: cytarabine; VP16: etoposide; Tenip: teniposide; VCR: vincristine.*

VCR also showed a synergistic effect when it was added to DTIC, cyclophosphamide, hydroxyurea and cisplatin. Each of these drugs had some survival gains in cohorts without VCR and adding VCR to them further improved the outcomes. In contrast, some drugs, including cytarabine and etoposide decreased the effect of VCR significantly. The complexity of drug interactions may help explain the poor results of the 8-in-1 regimen (24); the overall effect of eight drugs combined in one day was no survival gain.

Temozolomide is the standard single-agent first-line treatment for adults with glioblastoma (1, 5). Bevacizumab was recently licensed to treat recurrent disease; however, a standard of care for salvage therapy is not yet clear (25). As a result, patients with recurrent disease after temozolamide based treatment will be likely to comprise the majority of HGG patient population in the near future. VCR may be a valuable component in regimens for such patient groups, considering its efficacy in adult and elderly groups.

HGGs are one of the most challenging types of case in current oncology practice (1-18, 22-25). Every published study increases the experience of treating patients with HGG. Each of these experiences contributes to the efforts of developing and refining effective chemotherapy regimens and improving survival. The success of these efforts greatly depends on previous experiences with and knowledge of effective drugs or drug combinations on specific types of tumors.

In this study, the outcome of more than 40,000 chemotherapy-treated patients with HGG was evaluated, including small patient groups. According to the results, VCR can be recommended for both first-line and relapse regimens in the treatment of HGG. Drug interactions and their effects should be considered in multi-drug regimens. The data suggest that VCR should not be combined with BCNU, ACNU, cytarabine or etoposide. However, adding VCR to Cyc, DTIC, hydroxyurea or cisplatin may provide survival benefits. VCR seems to have potential benefit in combination therapies and deserves to be studied further in those combinations which appear synergistic.

References

1 Stupp R, Mason WP, van den Bent MJ, Weller W, Fisher B, Taphoorn MJB, Belanger K, Brandes AA, Marosi C, Bogdahn U, Curschmann J, Janzer RC, Ludwin SK, Gorlia T, Allgeier A, Lacombe D, Cairncross JG, Eisenhauer E and Mirimanoff RO: Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med *352(10)*: 987-996, 2005.

2 Huncharek M, Kupelnick B and Bishop D: Platinum analogues in the treatment of recurrent high grade astrocytoma. Cancer Treat Rev *24(5)*: 307-316, 1998.

3 Goerne R, Bogdahn U and Hau P: Procarbazine – a traditional drug in the treatment of malignant gliomas. Curr Med Chem *15(14)*: 1376-1387, 2008.

4 Wolff JE, Berrak S, Koontz Webb SE and Zhang M: Nitrosourea efficacy in high-grade glioma: a survival gain analysis summarizing 504 cohorts with 24193 patients. J Neurooncol *88(1)*: 57-63, 2008.

5 Stupp R, Dietrich PY, Ostermann Kraljevic S, Pica A, Maillard I, Maeder P, Meuli R, Janzer R, Pizzolato G, Miralbell R, Porchet F, Regli L, de Tribolet N, Mirimanoff RO and Leyvraz S: Promising survival for patients with newly diagnosed glioblastoma multiforme treated with concomitant radiation plus temozolomide followed by adjuvant temozolomide. J Clin Oncol *20(5)*: 1375-1382, 2002.

6 Wick A, Pascher C, Wick W, Jauch T, Weller M, Bogdahn U and Hau P: Rechallenge with temozolomide in patients with recurrent gliomas. J Neurol *256(5)*: 734-741, 2009.

7 Jeremic B, Shibamoto Y, Gruijicic D, Milicic B, Stojanovic M, Nikolic N, Dagovic A and Aleksandrovic J: Combined treatment modality for anaplastic oligodendroglioma: a phase II study. J Neurooncol *43(2)*: 179-85, 1999.

8 Bertolone SJ, Yates AJ, Boyett JM, Wallace D, Finlay JL; Children's Cancer Group: Combined modality therapy for poorly differentiated gliomas of the posterior fossa in children: a Children's Cancer Group report. J Neurooncol *63(1)*: 49-54, 2003.

9 Levin VA, Hess KR, Choucair A, Flynn PJ, Jaeckle KA, Kyritsis AP, Yung WK, Prados MD, Bruner JM, Ictech S, Gleason MJ and Kim HW: Phase III randomized study of postradiotherapy chemotherapy with combination alpha-difluoromethylornithine-PCV *versus* PCV for anaplastic gliomas. Clin Cancer Res *9(3)*: 981-990, 2003.

10 Geyer JR, Sposto R, Jennings M, Boyett JM, Axtell RA, Breiger D, Broxson E, Donahue B, Finlay JL, Goldwein JW, Heier LA, Johnson D, Mazewski C, Miller DC, Packer R, Puccetti D, Radcliffe J, Tao ML, Shiminski-Maher T; Children's Cancer Group: Multiagent chemotherapy and deferred radiotherapy in infants with malignant brain tumors: a report from the Children's Cancer Group. J Clin Oncol *23(30)*: 7621-7631, 2005.

11 Cairncross G, Berkey B, Shaw E, Jenkins R, Scheithauer B, Brachman D, Buckner J, Fink K, Souhami L, Laperierre N, Mehta M and Curran W: Phase III trial of chemotherapy plus radiotherapy compared with radiotherapy alone for pure and mixed anaplastic oligodendroglioma: Intergroup Radiation Therapy Oncology Group Trial 9402. J Clin Oncol *24(18)*: 2707-2714, 2006.

12 Levin VA, Silver P, Hannigan J, Wara WM, Gutin PH, Davis RL and Wilson CB: Superiority of post-radiotherapy adjuvant chemotherapy with CCNU, procarbazine, and vincristine (PCV) over BCNU for anaplastic gliomas: NCOG 6G61 final report. Int J Radiat Oncol Biol Phys *18(2)*: 321-324, 1990.

13 Hauch H, Sajedi M and Wolff JE: Treatment arms summarizing analysis of 220 high-grade glioma studies. Anticancer Res *25(5)*: 3585-3590, 2005.

14 Levin VA, Wara WM, Davis RL, Vestnys P, Resser KJ, Yatsko K, Nutik S, Gutin PH and Wilson CB: Phase III comparison of BCNU and the combination of procarbazine, CCNU, and vincristine administered after radiotherapy with hydroxyurea for malignant gliomas. J Neurosurg *63(2)*: 218-223, 1985.

15 Burton EC and Prados MD: Malignant gliomas. Curr Treat Options Oncol *1(5)*: 459-468, 2000.

16 Kappelle AC, Postma TJ, Taphoorn MJ, Groeneveld GJ, van den Bent MJ, van Groeningen CJ, Zonnenberg BA, Sneeuw KC and Heimans JJ: PCV chemotherapy for recurrent glioblastoma multiforme. Neurology *56(1)*: 118-120, 2001.

17 Murphy C, Pickles T, Knowling M and Thiesse B: Concurrent modified PCV chemotherapy and radiotherapy in newly diagnosed grade IV astrocytoma. J Neurooncol *57(3)*: 215-220, 2002.

18 Ron IG, Gal O, Vishne TH and Kovner F: Long-term follow-up in managing anaplastic astrocytoma by multimodality approach with surgery followed by postoperative radiotherapy and PCV-chemotherapy: phase II trial. Am J Clin Oncol *25(3)*: 296-302, 2002.

19 Jackson DV Jr., Sethi VS, Spurr CL, Willard V, White DR, Richards F 2nd, Stuart JJ, Muss HB, Cooper MR, Homesley HD, Jobson VW and Castle MC: Intravenous vincristine infusion: phase I trial. Cancer *48(12)*: 2559-2564, 1981.

20 Kellie SJ, Koopmans P, Earl J, Nath C, Roebuck D, Uges DR and De Graaf SS: Increasing the dosage of vincristine: a clinical and pharmacokinetic study of continuous-infusion vincristine in children with central nervous system tumors. Cancer *100(12)*: 2637-2643, 2004.

21 Stewart DJ: A critique of the role of the blood-brain barrier in the chemotherapy of human brain tumors. J Neurooncol *20(2)*: 121-139, 1994.

22 Chastagner P, Kalifa C, Doz F, Bouffet E, Gentet JC, Ruchoux MM, Bracard S, Desandes E and Frappaz D: Outcome of children treated with preradiation chemotherapy for a high-grade glioma: results of a French Society of Pediatric Oncology (SFOP) Pilot Study. Pediatr Blood Cancer *49(6)*: 803-807, 2007.

23 Brandes AA, Turazzi S, Basso U, Pasetto LM, Guglielmi B, Volpin L, Iuzzolino P, Amistà P, Pinna G, Scienza R and Ermani M: A multidrug combination designed for reversing resistance to BCNU in glioblastoma multiforme. Neurology *58(12)*: 1759-1764, 2002.

24 Finlay JL, Boyett JM, Yates AJ, Wisoff JH, Milstein JM, Geyer JR, Bertolone SJ, McGuire P, Cherlow JM, Tefft M, Turski PA, Wara WM, Edwards M, Sutton LN, Berger MS, Epstein F, Ayers G, Allen JC and Packer RJ: Randomized phase III trial in childhood high-grade astrocytoma comparing vincristine, lomustine, and prednisone with the eight-drugs-in-1-day regimen. Children's Cancer Group. J Clin Oncol *13(1)*: 112-123, 1995.

25 Buie LW and Valgus J: Bevacizumab: a treatment option for recurrent glioblastoma multiforme. Ann Pharmacother *42(10)*: 1486-1490, 2008.

Received December 23, 2009
Revised April 2, 2010
Accepted April 14, 2010