Etoposide Improves Survival in High-grade Glioma: A Meta-Analysis

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Abstract. *Background: The purpose of this meta-analysis was to evaluate the therapeutic efficacy of topoisomerase inhibitors in the treatment of high-grade gliomas (HGGs). Materials and Methods: Using median overall survival (mOS) and survival gain, we compared the efficacy of chemotherapy drugs in a meta-analysis of 624 HGG studies, including 44,850 patients from studies published between 1976 and 2011. Results: Patient cohorts treated with etoposide had significant improvement in mOS (15.66 months vs. 13.27 months, p=0.026, 49 vs. 795 cohorts) and significant survival gain advantage (p=0.022) over cohorts treated without etoposide. In contrast, patient cohorts treated with irinotecan had significantly worse mOS (10.20 vs. 13.55 months, p=0.008, 35 vs. 810 cohorts) and a disadvantage compared to cohorts treated without irinotecan in survival gain analysis. Conclusion: Results from this analysis suggest that etoposide may improve overall survival for patients with HGG, whereas the use of irinotecan might result in inferior outcomes.*

High-grade gliomas (HGGs) are the most common and aggressive group of primary central nervous system (CNS) tumors, characterized by diffuse parenchymal infiltration, extensive tumor necrosis, and prominent angiogenesis. Despite improved survival with surgical resection followed by radiation therapy (RT) and temozolomide chemotherapy, survival remains poor with a median overall survival (mOS) of only 14.6 months and a 2-year survival rate of 26% (1). Despite the addition of bevacizumab at onset and at disease recurrence, few treatments extend 6-month progression-free survival (PFS) beyond 21% (2, 3). In the pediatric population, CNS tumors account for 20% of all pediatric cancers and are the leading cause of cancer-related death and morbidity in children. Whereas RT and temozolomide have shown superior outcomes compared to RT-alone in adults, the use of temozolomide in the treatment of children with HGGs has had disappointing results, with mOS no greater than nine months (4, 5) and a 4-year survival of approximately 4% (6).

Although FDA-approved therapies have been shown to improve survival, patients ultimately succumb to their disease, and, thus, a need for novel regimens exists. A strong biological plausibility, good bioavailability, and low toxicity make topoisomerase inhibitors promising candidates for investigation in phase I and II trials. This group of antineoplastic agents is cell-cycle-dependent and cycle-phase-specific, and includes irinotecan, topotecan, etoposide, and teniposide. The heterogeneity of HGGs suggests that combination regimens exerting antitumor effects through different targets may be successful in overcoming drug resistance and increasing anti-tumor efficacy. As topoisomerases are involved in DNA repair mechanisms, various combinations with DNA alkylating agents have been tested (7).

Several studies have explored the antitumor activity of topoisomerase inhibitors alone and in combination with approved therapies in the treatment of HGG (8-16). Bevacizumab has been originally reported to achieve dramatic radiographic responses when combined with irinotecan among patients with glioblastoma (GBM) (17). Continuous intravenous (*i.v.*) infusion of topotecan has shown synergistic effect with RT in pediatric and adult CNS malignancies (18). Etoposide has shown synergistic activity with cisplatin in recurrent malignant glioma, with a partial response rate of 21% and mOS of 11.7 months (19).

Currently there are numerous phase II trials investigating novel therapies, with many agents and multi-agent combinations being tested in small series, some with striking preliminary data. However, it is difficult to directly compare patient cohorts and effectively rank which therapies may succeed in subsequent phase III clinical trials when study populations differ so drastically in factors such as age, performance status, previous treatments, and therapeutic regimen. Using a previously developed and published novel meta-analysis method that summarizes single patient cohorts from over 500 studies (20), we investigated the therapeutic efficacy of topoisomerase inhibitors in the treatment of

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HGG. Using a mathematical model to normalize outcomes via information provided in the published description of the patient populations, we sought to establish a drug ranking based on efficacy, therefore helping to predict value for the use of irinotecan, topotecan, etoposide, or teniposide in future phase III clinical trials as well as in the clinic.

Materials and Methods

Literature search. This study utilized and updated a pre-existing database of articles published on HGGs. At the start of the study, the database consisted of phase I, phase II, and phase III articles published between 1976 and April 2005 (20-22). A new literature search was performed spanning May 2005 to June 2011 using the PubMed database. The search terms included: high-grade glioma, glioblastoma (GBM), anaplastic astrocytoma (AA), brain stem glioma (BSG), anaplastic oligodendroglioma, or anaplastic oligoastrocytoma; phase I, phase II, phase III; radiation, radiotherapy, irradiation, chemotherapy, chemotherapeutic, etoposide, irinotecan, topotecan, camptothecin, doxorubicin, epipodophyllotoxin, podophyllotoxin. Additional limits included: abstracts, Humans, Clinical Trial, Meta-Analysis, Randomized Controlled Trial, Classical Article, Clinical Trial Phase I, Clinical Trial Phase II, Clinical Trial Phase III, Clinical Trial Phase IV, Comparative Study, Controlled Clinical Trial, Corrected and Republished Article, English Abstract, Multicenter Study, English, Cancer, and Publication Date 2005 to 2011.

Selection criteria. Abstracts that fulfilled the above criteria were reviewed for entry into the database. Every published English-language article that described a population of three or more patients with HGG and reported outcome data was selected, including populations with mixed characteristics (*i.e.* from all ages or all known HGG types). Outcome data consisted of response evaluation, median progression-free survival (mPFS), or mOS. Abstracts for which no article was later published in a peer-reviewed journal, articles that reported only laboratory data, and articles that did not report outcome descriptions were excluded. When comparison arms were duplicated across studies, only new data was entered into the database. If a given study consisted of more than one characteristic with accompanying outcome data for those separate groups (*i.e.* randomized studies with multiple arms, studies with more than one histopathological group with corresponding outcome data), the separate patient groups were entered into the database on separate lines to represent different patient cohorts.

Data reviewed. The database consisted of 333 variables. Reference information (seven columns) encompassed author, year, and other publication information. Patient cohort characteristics (37 columns) encompassed age, gender, tumor grade, tumor location, and previous treatments. Treatment (99 columns) documented surgery, radiation, and chemotherapy regimens. Outcome (44 columns) included treatment toxicity, details of response to treatment, PFS, and survival rates. Data entry (six columns) encompassed data source, and persons entering and reviewing data. Mathematical calculations (140 columns) included data on predicted OS and survival gain analysis. The details of the data structure and data entry rules are described in a Standard Operating Procedure (SOP) which can be made available by the senior author.

Table I. *Number of patient cohorts with topoisomerase inhibitor-containing regimens for the entire database and in subgroup analysis.*

	Number of patient cohorts (%)
Entire database	112 (12.6)
Topotecan	19 (2.1)
Irinotecan	35 (3.9)
Etoposide	49 (5.5)
Teniposide	9 (1.0)
Newly diagnosed	56 (6.3)
Recurrent or progressive disease	54 (6.1)
Pediatric-only	28 (3.2)
Adult-only	65 (7.3)
GBM-only	35 (3.9)
AA-only	6 (0.7)
With radiation	51 (5.7)
With other agents	86 (9.7)
With bevacizumab	16 (1.8)
With temozolomide	11 (1.3)
As a single-agent	19 (2.1)

GBM: Glioblastoma multiforme; AA: anaplastic astrocytoma.

Outcome measures. We chose mOS as the primary outcome measure. The mOS was defined by publication data or as a newly calculated value based on the 1-, 2-, or 5-year OS; mPFS; 6-month-, 1-, 2-, or 5- year PFS; or response rates. As previously described, values were calculated using multiple linear regression weighted by the square root of the number of patients (20), and predicted mOS was determined by multiple regression analysis, and known prognostic parameters as ranked by Pearson's correlation. The difference between predicted outcome and observed outcome for each cohort was defined as survival gain, as tested and validated in the previous report. Positive values for survival gain are a measure of the success of the treatment, whereas negative values indicate potential harm from treatment.

Statistical analysis. Two-tailed independent sample t-tests were used to detect a statistically significant difference between the mean values of mOS and survival gain. Statistical analysis was run on the entire dataset and then on selected subgroups as specified in Table I. 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.

Results

At the start of the project, the database consisted of 434 published articles. After the above selection for publications, 198 articles were added, totaling in 632 publications, 900 patient cohorts, and 45,258 patients. After excluding entries as described above, the total number of patients eligible for analysis was 44,850 in 888 cohorts from 624 publications (Figure 1).

Information regarding age and tumor status is listed in Figure 1. Gender was available in 585 cohorts (65.9%) for a

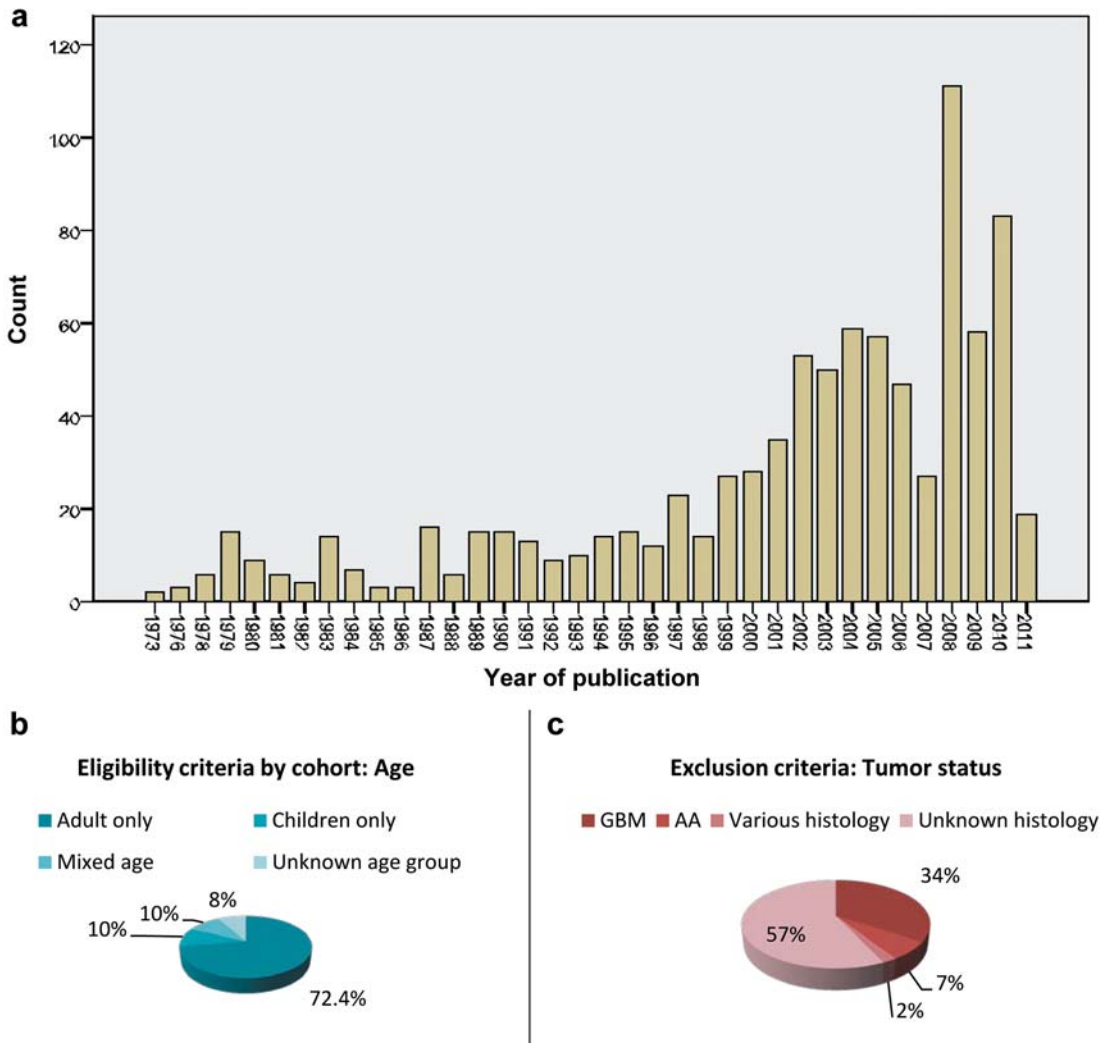


Figure 1. *Demographic data. a: Number of patient cohorts published per year. The total number of patients eligible for analysis was 44,850 patients in 888 cohorts from 624 publications. b: Distribution of age groups among patient cohorts. The mean of median patient age was 46.5 (SD=15.3 years; range=0-99 years). The majority of the patient cohorts consisted of adult only populations (637 cohorts), whereas 85 cohorts were pediatric only (age<17 years), 85 cohorts were considered mixed aged cohorts, and in the remaining 93 cohorts information regarding age was missing. c: Distribution of histological type among patient cohorts. Histological data were documented for 40,680 patients (90.7%). There were 32,335 patients with glioblastoma (GBM) and 6,358 patients with anaplastic astrocytoma (AA). The remaining 1,987 patients with histological data had either undistinguished GBM/AA, grade III mixture, or other mixture of both without clear subgroup differentiation.*

total of 18,350 male and 11,506 female patients (ratio=1.6:1). Localizations were documented in 40% of patients. In those, tumors were located in the supratentorial region in 15,838 patients, infratentorial region in 822 patients, brainstem (including the pons) in 1,131 patients, and along the spinal column in 66 patients. The average of the median Karnofsky score was 73.4 from 375 documented cohorts (SD=15.8; range=20-100).

Patients had prior radiation in 285 cohorts (32.1%) or prior chemotherapy in 169 cohorts (19.0%). Surgery was reported as part of the treatment in 375 cohorts (25,778 patients, 57.4%), with gross total resection in 6,568 patients (25.5%), partial resection in 10,008 patients (38.8%), and biopsy or no resection in 9,202 patients (35.7%). Radiation was reported as part of the treatment in 28,935 patients (64.5%), predominantly as conventional fractionated radiation in 362 cohorts (41.2%). Single-agent chemotherapy was documented in 354 cohorts (40.2%), whereas multiple-agent chemotherapy regimens were documented in 320 cohorts (36.3%). When evaluating the database for response, 456 cohorts (51.4%) had outcome data that were specific for a response to chemotherapy; 218 cohorts (24.5%) to

radiation; 236 cohorts (26.6%) to the combination of chemotherapy and radiation; and 232 cohorts (26.1%) to other treatment (non-chemotherapeutic agents such as monoclonal antibodies, anti-coagulants, anti-angiogenic agents, photo-/radio- sensitizers, *etc.*).

The mOS time was 13.3 months (SD=10.7 months, reported in 685 cohorts) and the mPFS was 6.9 months (SD=7.4 months, reported in 384 cohorts). After imputation of missing mOS values, the mean of the new mOS was 13.6 months (SD=10.2 months). Curve fit analysis was performed on the observed *vs.* expected mOS as calculated by the mathematical model to validate the prediction outcomes model.

Known predictive factors for outcome were evaluated in the data for two purposes: to validate the data set by comparing it to generally accepted information, and to improve the models of imputation for the subsequent treatment-related questions. The mOS was found to be significantly correlated with the percentage of tumors resected in a given cohort, median patient age, percentage of newly-diagnosed patients, percentage of children, percentage of patients who received RT, total radiation dose, and percentage of patients with WHO grade IV histology. All of these correlations were related to *p*-values of less than 0.0001. There was also a correlation to the percentage of male patients with a lesser *p*-value ($p=0.01$).

Topoisomerase inhibitor-containing regimens with either topotecan, irinotecan, etoposide, or teniposide were used in 112 cohorts (12.6%) (Table I). The mOS and survival gains for cohorts treated with topoisomerase-containing *vs.* non-containing regimens are listed in Figure 2. Results were significant for irinotecan-containing regimens [mOS=10.2 months *vs.* 13.6 months ($p=0.008$)], and etoposide-containing regimens [mOS=15.7 months *vs.* 13.3 months ($p=0.026$) and survival gain +1 months *vs.* –0.3 months ($p=0.022$)].

In subgroup analyses, the significance for efficacy of etoposide to improve mOS and provide a survival advantage over regimens without etoposide was confirmed for most subgroup definitions. This included subgroups of patients with newly-diagnosed tumors (mOS=18.4 *vs.* 15.1 months, $p=0.011$; survival gain 2.5 *vs.* –0.4 months, $p=0.021$), patients with GBM histology (mOS=11.9 *vs.* 11.4 months, $p=0.028$; survival gain not significant), patients treated with etoposide and bevacizumab (mOS=21.6 *vs.* 11.3 months, $p=0.008$; survival gain –0.1 *vs.* –5.8 months, $p=0.004$), and patients treated with radiation (mOS=18.2 *vs.* 15.0 months, $p=0.042$; survival gain not significant) (Table II). The significance for a survival disadvantage of irinotecan-containing regimens over non-irinotecan-containing regimens was confirmed for adult patients (mOS=9.8 *vs.* 13.0 months, $p=0.02$), for patients with GBM histology (mOS=10.2 *vs.* 11.5 months, $p=0.01$), and for patients treated with multiple agents (mOS=10.6 *vs.* 16.0 months, $p=0.006$; survival gain –0.9 *vs.* –0.2 months, $p=0.016$). Teniposide treatment resulted in a significant survival gain in subgroup analysis for adult patients only (4.0 *vs.* –0.6 months, $p=0.05$).

Discussion

Our study was aimed at investigating the efficacy of topoisomerase inhibitors in the treatment of HGG. In a large meta-analysis summarizing 624 publications with 44,850 patients, it was found that patient cohorts treated with etoposide had a significant improvement in survival over cohorts not treated with etoposide. In contrast, patient cohorts treated with irinotecan had a significantly inferior survival compared to cohorts not treated with irinotecan. For those two drugs, the database was large enough to validate the finding in various subgroups analyses. Furthermore, adult patient cohorts treated with teniposide showed a significant survival gain advantage over patient cohorts not treated with teniposide on subgroup analysis despite limited published data. Lastly, our data does not support the existence of substantial clinical activity of topotecan against HGG, consistent with the published data (23-26).

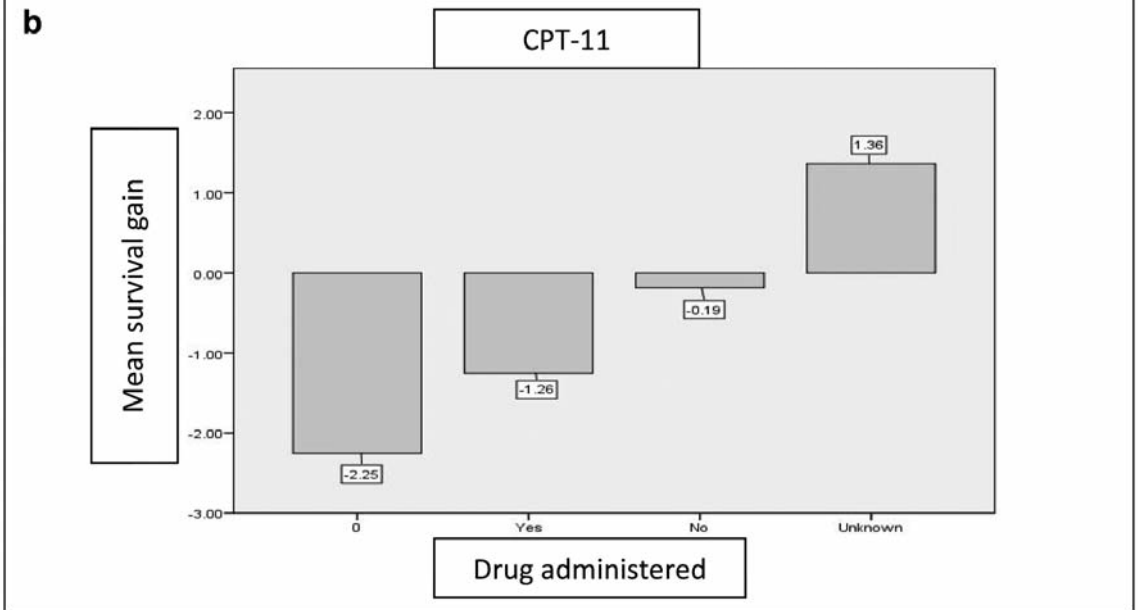
Our data was most revealing for the efficacy of etoposide-containing regimens (dose range 25 mg/m^2/d-1500 mg/m^2/d, the majority utilizing 50 mg/m^2 or 100 mg/m^2, either in the first three days of a cycle or for the first 21 days of a 28-day cycle). Despite statistical significance, the clinical significance is smalll: our data showed only a two-month gain in OS, consistent with data showing only moderate, but significant success among patients with recurrent malignant glioma (27-29). While etoposide appears to impart a small survival advantage to the group as a whole, in subgroup analysis, addition of VP-16 did not result in a significant mOS advantage for newly-diagnosed children, children with recurrent disease, newly-diagnosed adults, nor adults with recurrent disease. Despite not achieving statistical significance, a trend toward advantage existed for all but children with recurrent disease, which only had two studies that met criteria for etoposide use in children with recurrent disease. It is important to note that this database includes brainstem glioma, a uniformly devastating, aggressive, primarily pediatric disease that is not always confirmed histologically, and the inclusion of such may alter outcome analysis. Despite this, and despite subgroup analysis for the pediatric cohort not achieving significance, the likelihood of a significant survival advantage in the pediatric population given adequate power, is reasonable given the knowledge that etoposide has proven activity against medulloblastoma (30), supratentorial (31), and low-grade and HGGs (29, 32, 33) in pediatric patients.

The data suggest that etoposide may impart a small survival advantage, and anecdotally, physicians may offer it as a last resort at disease recurrence. With recent FDA

a

	N+	N-	mOS+	mOS-	*p*-Value	SG+	SG-	*p*-Value
TPT	19	822	11.7	13.5	0.232	-1.5	-0.2	0.315
CPT-11	35	810	10.2	13.5	**0.008**	-1.3	-0.2	0.183
VP-16	49	795	15.7	13.3	**0.026**	1.0	-0.3	**0.022**
VM-26	9	837	19.5	13.3	0.227	2.2	-0.3	0.120

b



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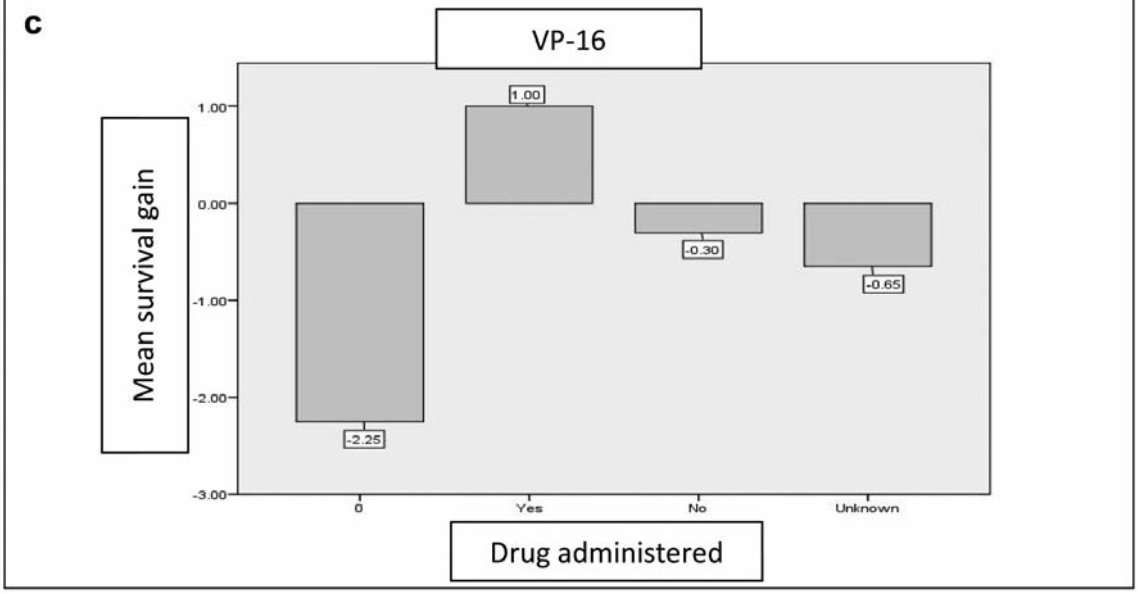

Figure 2. *Number of patient cohorts (N), median overall survival (mOS), and survival gain (SG) analysis for therapy with topotecan (TPT), irinotecan (CPT-11), etoposide (VP-16), and teniposide (VM-26). a: Outcome data after analysis on the entire database regarding number of cohorts, mOS, and SG in months for treatment regimens with each topoisomerase inhibitor. Survival gain analysis for b: CTP-11 and c: VP-16 calculated from the entire database inclusive of all treatment regimens (0), regimens using individual topoisomerase inhibitors (yes), regimens not using topoisomerase inhibitors (no), and regimens where data regarding topoisomerase inhibitors was not included upon entry in the database (unknown). The difference between predicted outcome and observed outcome for each cohort was defined as 'survival gain' indicating success or failure of treatment, as previously described (20).*

Table II. *Subgroup analysis: number of patient cohorts (N), median overall survival (mOS), and survival gain (SG) analysis for topotecan, irinotecan, etoposide, and teniposide.*

Newly-diagnosed									Recurrent or progressive disease							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	13	474	13.1	15.4	0.184	0.5	–0.3	0.191	6	325	4.9	9.4	0.758	–6.3	–3.5	0.667
CPT-11	5	482	14.0	15.3	0.205	–1.0	–0.2	0.407	29	305	7.0	9.5	0.168	–3.9	–3.7	0.238
VP-16	30	457	18.4	15.1	0.011	2.5	–0.4	0.021	18	316	8.8	9.3	0.766	–0.6	–3.8	0.683
VM-26	8	480	20.1	15.2	0.306	2.2	–0.3	0.158	1	334	14.3	9.3	*	–12.1	–3.6	*
Children									Adults							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	6	75	14.3	15.9	0.233	–2.4	–0.6	0.811	10	594	12.1	12.9	0.709	–0.1	–0.5	0.367
CPT-11	2	79	16.4	15.8	0.210	–3.9	–0.3	0.964	27	580	9.8	13.0	0.023	–1.4	–0.5	0.227
VP-16	20	61	16.5	15.6	0.061	–0.6	–0.3	0.117	21	585	15.8	12.5	0.642	1.0	–0.6	0.308
VM-26	0	82	–	15.8	*	–	–0.3	*	7	600	21.9	12.7	0.072	4.0	–0.6	0.053
Adults newly-diagnosed									Adults recurrent or progressive disease							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	8	338	13.8	14.5	0.499	1.2	–0.8	0.239	2	245	5.6	9.7	0.300	–5.5	–5.9	0.255
CPT-11	2	344	12.0	14.5	0.482	–0.7	–0.8	0.483	25	225	9.8	9.8	0.254	–8.2	–5.6	0.100
VP-16	11	335	17.9	14.4	0.584	0.9	–0.9	0.397	10	240	12.6	9.5	0.529	–3.9	–6.0	0.783
VM-26	6	340	23.1	14.4	0.099	3.9	–0.9	0.092	1	250	14.3	9.6	*	2.0	–6.0	*
Children newly-diagnosed									Children recurrent or progressive disease							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	3	57	7.4	13.9	0.505	–3.4	–3.1	0.554	3	15	12.5	13.8	0.163	–1.8	–2.2	0.609
CPT-11	1	59	16.5	13.5	*	–11.0	–3.0	*	0	18	–	13.5	*	–	–2.1	*
VP-16	18	42	14.1	13.3	0.118	–2.4	–3.3	0.139	2	16	8.9	14.2	0.161	–2.0	–2.1	0.601
VM-26	0	61	–	13.5	*	–	3.1	*	0	18	–	13.5	*	–	–2.1	*
Glioblastoma multiforme									Anaplastic astrocytoma							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	8	340	12.3	11.4	0.616	–0.7	–0.2	0.858	0	61	–	21.2	*	–	–2.8	*
CPT-11	16	333	10.2	11.5	0.010	0.4	–0.2	0.023	2	59	6.9	21.6	0.158	–3.0	–2.8	0.509
VP-16	9	340	11.9	11.4	0.028	0.5	–0.2	0.206	3	58	20.0	21.3	0.716	1.5	–3.1	0.520
VM-26	2	347	12.9	11.4	0.794	–0.2	–0.2	0.562	1	60	60.0	20.5	*	30.0	–3.4	*
With bevacizumab									With temozolomide							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	0	24	–	12.2	*	–	–5.3	*	1	156	15.3	12.0	*	2.4	–1.6	*
CPT-11	14	10	10.7	14.2	0.137	–7.2	–2.7	0.217	6	15	8.8	12.1	0.599	–4.8	–1.4	0.183
VP-16	2	22	21.6	11.3	0.008	–0.1	–5.8	0.004	4	153	10.5	12.1	0.247	1.0	–1.6	0.473
VM-26	0	24	–	12.1	*	–	–5.3	*	0	157	–	12.0	*	–	–1.5	*
With radiation									With other agents							
	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	12	465	12.5	15.3	0.208	0.2	–0.1	0.305	5	301	10.9	15.7	0.432	–5.8	–0.2	0.388
CPT-11	4	473	14.8	15.2	0.265	1.4	–0.1	0.974	26	283	10.6	16.0	0.006	–0.9	–0.2	0.016
VP-16	28	448	18.2	15.0	0.042	2.6	–0.3	0.146	46	262	15.6	15.5	0.880	–1.4	–0.1	0.581
VM-26	7	470	21.1	12.1	0.151	3.6	–0.2	0.129	9	299	19.5	15.5	0.623	–0.4	–0.3	0.376

Table II. *Continued*

Table II. *Continued*

As a single-agent

	N+	N–	mOS+	mOS–	*p*-Value	SG+	SG–	*p*-Value
TPT	14	335	12.0	12.4	0.673	0.2	–0.3	0.058
CPT-11	9	341	9.4	12.5	0.425	–5.0	–0.2	0.589
VP-16	3	347	9.7	12.4	0.664	–5.7	–0.2	0.473
VM-26	0	350	–	12.4	*	–	–0.3	*

TPT: Topotecan; CPT-11: irinotecan; VP-16: etoposide; VM-26: teniposide; N+: number of studies with treatment regimens that contain the therapeutic agent; N–: number of studies with treatment regimen that do not contain the therapeutic agent; mOS+: mOS for studies containing the therapeutic agent in the treatment regimen; mOS–: mOS for all other studies (without the therapeutic agent); SG+: gain in survival in months for studies containing the therapeutic agent in the treatment regimen; SG–: gain in survival in months for all other studies (without the therapeutic agent). The difference between predicted outcome and observed outcome for each cohort was defined as survival gain, as tested and validated in the previous report (20). Positive values for survival gain are a measure of the success of the treatment, whereas negative values indicate potential harm from treatment. *No data or data too limited to calculate significance values.

approval for bevacizumab, and given its use at disease recurrence, there are several studies investigating combination therapy of bevacizumab with etoposide. Such a combination has encouraging outcomes for patients with recurrent GBM, with 6-PFS rate and mOS higher than those reported with temozolomide at first recurrence (3, 12). Furthermore, daily etoposide is well-tolerated and does not increase bevacizumab-specific toxicity, whereas there are multiple reports describing toxicity of combined bevacizumab and irinotecan regimens, which resulted in discontinued therapy (8, 34). In children, the bevacizumab-irinotecan combination, related toxicity was mild, however no efficacy could be documented in patients with HGG, nor PNET, nor ependymoma (35). Friedman *et al*. reported objective response rates of 28.2% and 37.8% after bevacizumab and bevacizumab with irinotecan-containing regimens, however, mOS was only 9.2 months and 8.7 months, respectively (8), consistent with our observed trend toward a survival disadvantage in patients treated with this combination. Given these individual publications and results from this meta-analysis, etoposide may be a superior addition to bevacizumab as compared to irinotecan, although from our data set it is unclear if the advantage seen is from bevacizumab, etoposide, or the combination.

Our results regarding irinotecan were not surprising, as several phase II trials consistently demonstrated that single-agent irinotecan has minimal activity in newly-diagnosed, recurrent, or progressive HGG in adult patients (36-38). Out of these studies, two are large multi-institutional trials of single-agent irinotecan for recurrent glioma without prolongation of PFS. Conversely, a trend toward prolonged mOS that was not significant was seen in a pediatric cohort sub-group analysis and in newly-diagnosed pediatric cohorts. Since tumors of pediatric patients were found to respond differently to other drugs when compared to the same histological diagnoses in adult patients (4-6) (likely based on biological, genetic, and molecular differences, for example histone H3 mutations), this prolongation in OS may truly exist; however, further investigation, including adequate power upon investigative analysis, is needed before this can be concluded. Given recent data, however, irinotecan is unlikely to improve outcome over historical controls. A multicenter, two-stage phase II study investigating irinotecan plus temozolomide in children with newly-diagnosed HGG was stopped for futility after there were no complete or partial responses during the two-cycle treatment window in the first ten evaluable patients (39).

The inter- and intra-tumoral heterogeneity of gliomas suggests that a combination regimen may be efficacious in producing a lasting antitumor effect and overcoming drug resistance. Alkylating agents, such as temozolomide, and inhibitors of DNA repair, such as the topoisomerase inhibitors, are ideal candidates for combination chemotherapy because they exert antitumor effects through different targets, and have different organ toxicities. The significant improvement in mOS and the survival gain with etoposide, and the survival disadvantage with irinotecan may be related to their differing mechanisms of action within the drug class. Etoposide appears to induce single-stranded DNA breaks indirectly as opposed to irinotecan, which induces replication arrest directly. How these small differences in mechanisms of action affect tumor response is unknown and warrants further investigation, particularly separating adult and pediatric populations given known molecular differences.

The challenge in comparing the efficacy of treatment regimens for HGG is to compare various outcome parameters for different patient populations. This meta-analysis differs from existing models by summarizing phase I, phase II, and phase III studies, inserting missing survival variables as calculated by other outcome parameters and information

provided in the published description of the patient populations, and finally by performing a survival gain analysis in order to effectively combine and compare cohorts. While there are limitations inherent with meta-analysis, this model has proven useful for ranking drugs in their efficacy against HGG (20, 21), and was able to predict the results of Stupp *et al*. (1), yet refinement of this model may improve the method. In particular, accounting for treatment design is important and can have clinical significance. This study is limited by its absolute comparison of treatment regimens. Its inability to compare studies based on treatment design is important, as we know some drugs are more or less efficacious depending on when they are given in relation to other agents.

Inevitably, HGGs are one of the most formidable challenges faced by oncologists. There are enormous published and unpublished data regarding HGGs in many different patient populations, all of which works to further our knowledge, contribute to the efforts of developing and refining treatment, and ultimately improve survival. It starts with discovery science, to early phase I studies, to clinical trials, and ultimately to patient experience. Despite finding only an increase in survival of two months in this study, the ability to collate this vast body of information can only provide direction for future research, and ultimately, large or small, make advances in the field.

Conclusion

In this study, results from 44,850 patients from 624 studies of HGG were combined to assess the efficacy of topoisomerase inhibitors in the treatment of HGGs. Results suggest that etoposide improves OS and should be investigated in phase III trials and potentially included in chemotherapy regimens for HGG, whereas the use of irinotecan results in worse survival outcomes, and further investigation and use is unlikely to produce survival benefit.

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