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CLINICAL-PATIENT STUDIES

Nitrosourea efficacy in high-grade glioma: a survival gain analysis summarizing 504 cohorts with 24193 patients

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Abstract Even though past studies have suggested efficacy of nitrosourea drugs in patients with high-grade glioma and temozolomide has recently been shown significantly to be beneficial, no conclusive comparisons between these agents have been published. We performed a survival gain analysis of 364 studies describing 24,193 patients with high-grade glioma treated in 504 cohorts, and compared the effects of drugs. The most frequent diagnoses were glioblastoma multiforme (GBM) (72%) and anaplastic astrocytoma (22%). The mean overall survival (mOS) was 14.1 months. The outcome was influenced by several of the known prognostic factors including the histological grade, if the tumors were newly diagnosed or recurrent, the completeness of resection, patients' age, and gender. This information allowed the calculation of a predicted mOS for each cohort based on their prognostic factors independent of treatment. Survival gain to characterize the influence of treatment was subsequently defined and validated as the difference between the observed and the predicted mOS. In 62 CCNU-treated cohorts and 15 ACNU-treated cohorts the survival gain was 5.3 months and 8.9 months ($P < 0.0005$), respectively. No detectable survival gain for patients treated with various BCNU-containing regimens was found. *Conclusion* CCNU- and ACNU- containing regimens were superior to BCNU containing regiments.

Keywords Nimustine · Carmustine · Lomustine · Ranimustine · 1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl) · Glioblastoma multiforme · Survival gain

Abbreviations

ACNU	Nimustine
BCNU	Carmustine
CCNU	Lomustine
MCNU	Ranimustine
PCNU	1-(2-Chloroethyl)-3-(2,6-dioxo-3-piperidyl)
GBM	Glioblastoma multiforme
LC_{50}	Lethal concentration resulting in killing of 50% of cells
mOS	Median overall survival
MW	Molecular weight
SG	Survival gain
SPSS	Statistical package for social studies

Introduction

High-grade gliomas remain a therapeutic challenge. In the past, nitrosourea drugs such as carmustine (BCNU) and lomustine (CCNU) were the standard of care in addition to radiation. This has changed since temozolomide (TMZ)

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was shown to have benefit with less toxicity [1] and later studies focused on combinations of temozolomide with other drugs. The therapeutic value weight of the previously used drugs compared against temozolomide and to each other is still unknown Here we compare the other drugs, which could be possibly combined with TMZ.

In an analysis summarizing treatment arms we recently showed that these trials' outcomes are largely influenced by their eligibility criteria and epidemiological patient population's characteristics [2]. In this article we present a further development of the method aiming to evaluate single treatment results using the rest of the studies as control groups. We found that CCNU- and ACNU-containing regimens were superior to BCNU containing regimens.

Material and methods

This analysis expands upon a database that had been created for a treatment-arm-summarizing analysis by compiling information from the literature on high-grade glioma published from 1976 to 2002 [2]. This method generally falls under the umbrella of meta-analytic and meta-regression techniques [3]. For the current study, the previous database was reviewed, expanded to include more fields and the data from studies published through May 2005. The new expanded database contains 229 fields (rows), which include the following categories of items: reference (5 items, e.g., author and year), patient cohort characteristics (30 items, e.g., median age, tumor gradings, tumor locations, and previous treatments), treatment (145 items, e.g., surgery, radiation, and single drugs used), outcome (24 items, e.g., toxic death, response, median overall survival, and 1-year overall survival), and data entry characteristics (25 items, e.g., data source, person entering data, person reviewing data).

Eligibility criteria

This study aimed to avoid a selection bias. Every published English-language article that described a population of five or more patients with high-grade glioma was eligible. There was no patient age limit. Also eligible were studies describing populations with mixed characteristics, including other high-grade gliomas and pontine glioma, which are reported commonly in the pediatric literature. A study having used strict eligibility criteria, suggesting it had a highly selected study population, did not exclude the study from our database if the eligibility criteria were applied before the outcomes were known. After a review of abstracts, articles with missing outcome descriptions were excluded, along with articles that selected patients retrospectively based on known outcomes. In case of duplicate publications of the same patient cohort, only the most recent publication was used for further analysis. Abstracts which were published without complete article published in a peer reviewed journal were not included.

Data entry

As previously described, relevant literature was primarily identified using the PubMed database. Searches were performed with the following terms: glioma, glioblastoma, anaplastic astrocytoma, anaplastic oligodendroglioma, diffuse intrinsic pontine glioma, GBM, AA, AO, and DIPG. The data from the abstracts of published papers of each study that met our inclusion criteria were entered in the database. Complete papers were retrieved as often as possible and used to validate and fully complete each record. We repeated data entry to validate current data and limit internal error and reviewing the eligibility criteria again. Each record created was based on the review of study abstracts by a minimum of two people. Of the 504 cohorts finally used, 382 were documented based on full papers, 122 on abstracts of published papers. Abstracts which had been published without a full manuscript, such as abstracts of talks in meeting reports were not included.

Imputation of observed outcome

The first step involved imputing any missing median overall survival times based on the set of outcome variables thought to be correlated with outcome [4]. The choice of median overall survival time as the indicator of patient cohort outcomes was based on the treatment-arm-summarizing analysis [2]. Missing data for median overall survival were imputed using other outcome variables as previously described [2] such as one year overall survival, two or five year overall survival, progression free survival either as median or after defined time periods, or response. A hierarchy of outcome variables was developed based on how closely each variable was related to median overall survival, and in turn how useful each was in calculating median overall survival. For each missing median overall survival time, the highest-ranking, available variable in the hierarchy was used for imputation [2].

Defining predicted outcome

We estimated a second independent column of quantities for median overall survival times based on a set of key

predictive demographic variables and called this estimate the "predicted outcome." Predicted outcome was calculated for each cohort using a multiple linear regression weighted by the square root of the number of patients. With the exception of median age, all the other variables that are shown in Table 1 were expressed as percentage of the total number of patients of each cohort. These specific predictor variables were ranked according to their correlation with median overall survival as determined by Pearson's correlation coefficient and verified by weighted multiple linear correlations using the square root of the patient number as weight and SPSS 12.0 as program (Statistical Package for Social Studies, SPSS® Inc, San Francisco, Ca, USA). For each cohort, the predicted median overall survival was determined using various models based on multiple linear regression analyses and including as many parameters as possible. The first model was created using all ten parameters and those cohorts, which had all of them documented, calculating the predicted mOS only for those cohorts. The next model was created avoiding the parameter with the lowest ranking; it included the information of those nine parameters derived from the previously used 10-paramter-cohorts pooled with those that had only the nine documented. The model was used to fill the fields of predicted median overall survival only for cohort, which had only these nine parameters documented. The process was repeated until with the next set of nine parameters this time avoiding the second lowest ranking parameters, and filling in those missing values of predicted mOS which had not been calculated before with the stronger models. This process was repeated with gradually weaker models and less parameters until the fields for predicted mOS was filled for all cohorts. These predicted median overall survival times are dependent solely on the patient population, not on the treatment. It took into account the prognostic factors such as age at diagnosis and completeness of resection.

Using predicted outcome and observed outcome to define survival gain

The difference between the predicted outcomes and the observed or imputed outcomes is a measure of relative success of any particular treatment**.** We defined that difference to be "survival gain". This quantity describes the effect of treatment (because treatment is not used to estimate predicted outcomes) independent of the number of patients. For the following calculations, however, a large patient cohort should have a greater weight than a smaller cohort. Therefore, the "weighted survival gain" was calculated by multiplying the survival gain by the square root of the number of patients.

Testing the hypothesis

The above described methods contained several novel and disputable details. Their validity was therefore considered a hypothesis, which we tested predicting that the methods could show the benefit of temozolomide. This was done twice, first by simulating the eligibility criteria used in the defining phase III study, and then by broadening the eligibility criteria including further age groups and histological groups. In both tests the survival gain in studies with temozolomide was compared to those without any chemotherapy, using t-tests after excluding the large

Table 1 Characteristics of patient cohorts influencing median overall survival

Cohort characteristic	No. of patient cohorts	Pearson's correlation coefficient[a]	*P* value for Pearson test	*P* value for un-weighted multiple regression	*P* value for weighted multiple linear regression[b]	Rank[c]
Male (%)	275	−0.145	0.016	0.586	0.246	7
Median age (years)	373	−0.215	<0.0005	0.084	0.044	3
Children (%)	400	0.132	0.008	0.962	0.91	8
Newly diagnosed (%)	506	0.193	<0.0005	0.042	0.067	2
Supratentorial location (%)	242	0.76	0.241	0.142	0.144	10
Brain stem glioma (%)	246	−0.093	0.145	0.097	0.24	9
Grade IV histology (%)	442	−0.372	<0.0005	0.008	0.005	1
Other histologies (%)	439	0.212	<0.0005	0.940	0.649	6
Resections (%)	340	0.222	<0.0005	0.459	0.316	5
Gross total resections (%)	282	0.232	<0.0005	0.096	0.114	4

[a] Pearson's correlation coefficient indicates how closely the mOS correlated with the particular characteristic. Negative values indicate inverse relationships (having more men lowered survival)

[b] Cohorts weighted by the square root of the patient numbers to calculate *P* values

[c] The predictor variables were ordered by their correlation to mOS

defining phase III study with known outcome [1]. *P* values below 0.05 were considered significant.

Comparing various drugs

For each drug, the survival gain of all studies was averaged, in which the treatment protocol contained the drug. Positive survival gain indicates longer median overall survivals reported. The statistical significance of these differences may be determined in several ways. First, the cohorts that received the drug were compared to those that did not receive any chemotherapy using the Wilcoxon rank sum test for weighted survival gain. Second, the results from cohorts that received the drug were compared with those from a control group consisting of all the other cohorts, also including those that received different drugs. We consider this analysis observational, the *P* values descriptive.

Result

Description of the database

We had to exclude seven cohorts for the following reasons: useful outcome data were missing (three), patients were selected for poor outcomes (one), and patients were selected for good outcomes (three). The remaining 504 cohorts were extracted from 364 studies and described 24,193 patients (Table 1).

The median overall survival (mOS) was the most frequently reported outcome measure (377 cohorts). The mean of the median overall survival was 14.1 months (standard deviation [SD], 11.8 months). Imputing missing values resulted in a mean of 14 months (SD, 10.9) in 504 records. The sources for these calculations were 1-year overall survival from 45 cohorts, 2-year overall survival from 3, 5-year overall survival from 3, 6-month progression-free survival from 3, median progression-free survival from 22, response frequency (both complete and partial response) from 14, and frequency of progressive disease from 37. The influence of demographic patient cohort characteristics was analyzed first disregarding the treatment effect, which was to be analyzed later. We found the median overall survival influenced by the histological grade, if the tumors were newly diagnosed or recurrent, the completeness of resection, patients' age, and gender. After correcting for these biological parameters, multicenter studies and single center studies did not differ significantly in outcome. Some of those parameters were coded in various ways such as the patient's age distribution as median age and as percentage of patients under 18 years of age, but the outcomes were consistent (Table 1). The analysis was repeated excluding all imputed data with similar results (same ranking of influencing factors, smaller numbers, larger *P* values, data not shown) confirming the validity of the imputation. Similar to our previous analysis the documented median Karnofsky Index was 70 in most the published cohorts, without much variation and therefore also without correlation to outcome.

The predicted median overall survival for each cohort was generated relating the patient population characteristics (Table 1) and the correlation found to the observed outcome. The final calculation used all 10 items for 111 cohorts, nine items for 53, eight items for 49, six items for 27, five items for 25, four items for 71, three for 98, two for 59, and one for 11. The mean of the resulting predicted mOS was 13.52 months (SD, 5.15 months; range, 2.1−47.4 months). The difference between this predicted outcome and the observed outcome was the survival gain.

Validation of the survival gain concept

To determine whether survival gain indeed represents the effect of the treatment, the known effect of TMZ [1] was used as the gold standard, and the method validated based on the hypothesis that it would thus confirm the effect. The database included 17 cohorts whose patients received TMZ as part of their treatment for newly diagnosed high-grade glioma. We excluded the study that established the standard, and then compared the mOS from the remaining 16 cohorts that used temozolomide with the 69 patient cohorts in which patients with newly diagnosed high-grade glioma had not received any chemotherapy. Based on this subset of the data, our hypothesis was confirmed: the mean survival gain and the mean weighted survival gain were significantly higher in the studies, in which temozolomide had been used, than in the ones that had not used it. This was true regardless whether mOS or survival gain was used as the endpoint (Table 2). However, when the test was repeated including not only cohorts with newly diagnosed but also those with relapsed patients, the observed mean of the mOS times reported for non-temozolomide-receiving cohorts was greater than the mean of the mOS times for cohorts receiving temozolomide, wrongly suggesting no benefit for temozolomide. This changed once the effect of patient characteristics was accounted for in the estimation of survival gain: Cohorts that received temozolomide were estimated to achieve greater survival gain. Moreover, this difference reached a *P* value below 0.05 via the meta-regression of survival gain (Table 2). This analysis confirmed the hypothesis that the calculation of survival gain was capable of detecting treatment effects.

Table 2 Validation of database: confirming the known effects of temozolomide (TMZ)[a]

	No TMZ Newly diagnosed only	TMZ Newly diagnosed only	*P* value Comparing newly diagnosed TMZ versus no TMZ	No TMZ All diseases status	TMZ All disease status	P Comparing all diseases status TMZ vs no TMZ
No. of cohorts	69	16	–	105	52	–
mOS	11.5	14.9	0.003	12.8	12.0	0.90
Survival gain	−3.1	0.38	0.013	−1.1	−0.2	0.08
Weighted survival gain	−21.1	4.0	0.009	−9.7	−0.6	0.04

The first analysis was restricted to cohorts of patients with newly diagnosed tumors (newly diagnosed only, first three columns on left). The second analysis included all cohorts, those with newly diagnosed and those with relapsed tumors (all diseases status three columns on right). Both excluded the publication used to define the gold standard [1] as well as cohorts that received any chemotherapy other than TMZ. Imputation of mOS is described in materials and methods. *P* values are the result of the Wilcoxon Rank sum test

Comparing nitrosoureas

Given that the model was validated, we subsequently used it to compare effects of various nitrosoureas. In the literature, the use of certain nitrosoureas was preferred in certain populations (Table 3): BCNU was the most frequently used nitrosourea in adult patients, CCNU in children. Given the influence of patients' age on outcomes, a simple comparison of the means of the mOS times would be biased, which makes the calculation of survival gain necessary (Fig. 1). Based on our data, the highest survival gain were estimated for ACNU (8.9 months) and MCNU (7.7) followed by CCNU (5.3), Fortemustine (2.0) and PCNU (1.2), while BCNU, BCNU wafers, and CleNU provided no survival gain (−0.1, −2.3 and −2.5 months, respectively). The statistical significance of these differences was tested with the two methods described above for each drug individually. When comparing the cohorts treated with one of the drugs to those not treated with chemotherapy, only CCNU and ACNU had significant benefits ($P = 0.003$ and $P < 0.0005$, respectively). When comparing to all the other cohorts, the controls including those that received different drugs and those that received no chemotherapy, all *P* values changed slightly; but the only significantly superior treatments were unchanged those that included CCNU ($P = 0.019$) or ACNU ($P < 0.0005$).

Drug combinations

Nitrosoureas were frequently used in combination with other treatments. Therefore, outcomes of cohorts treated with a single drug were compared with drug combinations. No detectable difference was found between the BCNU-only and ACNU-only cohorts and the cohorts that received their respective combination regimens; however, the survival gain in cohorts that received combination treatments involving CCNU and MCNU appeared greater than the survival gain found in the cohorts that received their respective single-treatment regimens (not significant).

Discussion

In this analysis, we have found that treatment protocols containing CCNU and ACNU but not BCNU increased the

Table 3 Nitrosourea use in different populations

Drug	No. of cohorts	No. of patients	% Children	% with Newly diagnosed disease	% with Glioblastoma multiforme	% with Gross total resection	Mean of mOS times
All cohorts	504	24193	14	63.7	68.9	15.9	10.0
All nitrosoureas	177	10613	15	80.1	67.2	19.3	14.7
BCNU	81	5629	5.1	75.2	72.8	16.5	13.7
BCNU wafers	4	186	0	66.7	79.6	0	12.6
CCNU	62	3123	31.6	80.6	57.5	22.5	21.6
ACNU	15	758	8.6	100	69.3	19.6	8.9
MCNU	7	387	0	100	66.4	11.4	7.7
PCNU	5	306	0	40	55.6	4.2	13.9
Fortemustine	3	102	0	33.3	91.1	18.2	2.6
Chlorethylnitrosourea	1	37	0	0	38	0	9.0
No chemotherapy	105	5186	9.1	70.2	67.9	19.1	7.7

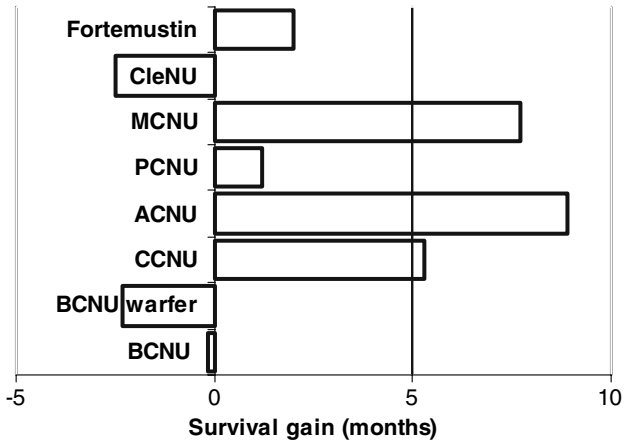

Fig. 1 Survival gain by nitrosoureas: The result of various mathematical steps described in materials and methods is the quantification of the benefit patients had from a drug expressed as live extension in months caused by the drug. The difference of the median survival predicted for a given patient population and the observed median survival with the treatment is expressed as survival gain. Bars to the right (+) represent treatment results which were better then the average of all publications, bars to the left (−) inferior treatments

survival of patients with high-grade glioma. Confirming previous results [2], we showed that the characteristics of the patient population had a substantial effect on the outcome (Table 1). Most of these findings were consistent with the findings generated from the analysis of data describing individual patients [5–9].

Although this survival gain analysis has some limitations, none of those created a major flaw as the method as a whole could be validated. Further refinements are therefore worth the effort. Obviously, expending the original data will improve the database, such as inclusion of newer studies published after the cutoff of May 2005. Also, other endpoint substituting mOS with for instance 10% survival time or with the area under the survival curve could sharpen this tool. Furthermore, in this study, each missing mOS was imputed using data from the complete studies. This single imputation for missing values does not reflect the uncertainty about the predictors of the unknown missing values, and the resulting variance of the estimated values will appear smaller. In a future analysis, we plan to test a multiple-imputation approach [10], which can be used not only to estimate the median overall survival time but also missing demographic predictor variables, and to also use the assumption of logarithmic as opposed to linear relation between outcome and influencing demographic variables. Also, the statistical testing framework could be simplified, and we plan to improve on the fixed-effects meta-analysis used here by performing random effects meta-analyses. The result of each of these possible optimizations of the method will need to be validated and compared to the result of the existing method described here. While these modifications are important and interesting, they go beyond the scope of this study, which aimed primarily to find the best nitrosoureas for the treatment of high-grade glioma.

Despite the limitations discussed above, we were able to validate the survival gain model as a whole by measuring its accuracy against the known effects of temozolomide. In comparing only cohorts with newly diagnosed tumors we found that the difference between cohorts that received temozolomide and those that received no chemotherapy was significant, which confirmed the validity. The results further suggest that the information about the beneficial effects of temozolomide had been available prior to the large phase III study [1]. However, this first validation test did not confirm the need for the other statistical steps. This need became more apparent in the second test when calculating based upon cohorts that also contained patients whose disease was recurrent (Table 2). In that analysis, the means of the reported median overall survival times wrongly suggested that the cohorts that not received temozolomide had the better outcome, but the normalized survival gain analysis suggested the drug had a benefit, and the weighted survival gain comparison indicated that finding was significant. This shows that those statistical steps are necessary to detect the value of treatment protocols when analyzing more heterogeneous patients' cohorts.

The overall outcome of high-grade glioma is poor. In our data this is documented with a mean overall survival (mOS) of only 14.1 months. This confirms the need for new research efforts including novel treatments but also novel ways to analyze the data, such as the approach taken here. The number of 14.1 months even appears lower than some of the more modern publications (23), which might reflect that there is indeed some progress, and which calls for caution, which conclusion can be drawn when comparing the numbers. In this analysis we compare drugs, each of them first compared separately to the predicted outcome. If there is a bias caused by general improvement, it will not affect the comparison of the drugs as each of them will be affected in the same way.

BCNU (carmustine; 1,3-Bis(2-chloroethyl)-1-nitrosourea, molecular weight: 214.05) was the most frequently used chorethylnitrosourea drug in brain tumors [18, 19]. However, we could not confirm any beneficial effects of BCNU on the median overall survival time of patients with high-grade glioma. This surprising finding could be explained by the nature of the endpoint mOS: If a group of patients has mostly non-responsive tumors, with only a minority having responsive tumors, this heterogeneity when graphed as survival curves of treated patients and controls, will be represented by a difference in the end of the cohort's survival curves, which represents the 10% survival times or the 5-year overall survival rates, but not in the 50% or mOS [11, 12].

CCNU (lomustine, 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea, molecular weight 233.70 has the same active group as BCNU attached to a slightly larger molecule. Treatments including this drug were more effective than those with BCNU in our analysis, which confirms the results of Levin and colleagues [13]. In our analysis it was difficult to isolate CCNU's effects when given alone from the effect when given as part of a combination regimen. It remains possible that the benefit measured here was largely caused by the most frequently used additive drugs, vincristine and procarbazine, and we plan to approach this question in the next generation of models again. Nonetheless, these data strongly suggest that CCNU, at least in the commonly used combinations, is a useful drug in the treatment of high-grade glioma.

MCNU (ranimustine, methyl 6-[3-(2-chloroethyl)-3-nitrosoureido]-6-deoxy-α-D-glucopyranoside; methyl CCNU, molecular weight 327.7) [14] is used as a modification of the "PCV- regimen" [15]. In our analysis, it had similar results as CCNU. Its lack of statistical significance can likely be related to the smaller number of cohorts treated with this molecule in published studies (Table 3), rather than the ineffectiveness of the drug (Fig 1).

ACNU (nimustine 3-[(4-Amino-2-methylpyrimidin-5-yl) methyl]-1-(2- chloroethyl)-1-nitrosourea hydrochloride, MW 309.2) is more selective than CCNU and BCNU in killing *MGMT*-deficient cells [16]. It was mostly given alone. Its survival gain was significant despite the relatively small number of cohorts treated with it. According to our analysis, ACNU leads the nitrosoureas in efficacy.

Fotemustine ((±)-diethyl [1-[3-(2-chloroethyl)-3-nitrosoureido]ethyl]-phosphonate, MW 315.69 [14] is a new nitrosourea drug that is reported to be less hepatotoxic [17] but for both fotemustine and chlorethylnitrosourea, our database analysis still contains too few cohorts for a meaningful analysis.

In conclusion, the survival gain analysis was validated by using it to confirm the known benefit of temozolomide. When comparing nitrosoureas, we could not confirm any benefit from BCNU for patients with high-grade glioma. CCNU, at least when given in common combination chemotherapy regimens, and ACNU both increased the survival time of patients with high-grade glioma.

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