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CASE STUDY

Patterns, predictors and prognostic relevance of high-grade hematotoxicity after temozolomide or temozolomide-lomustine in the CeTeG/NOA-09 trial

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Abstract

Purpose In the randomized phase III trial CeTeG/NOA-09, temozolomide (TMZ)/lomustine (CCNU) combination therapy was superior to TMZ in newly diagnosed MGMT methylated glioblastoma, albeit reporting more frequent hematotoxicity. Here, we analyze high grade hematotoxicity and its prognostic relevance in the trial population.

Methods Descriptive and comparative analysis of hematotoxicity adverse events ≥ grade 3 (HAE) according to the Common Terminology of Clinical Adverse Events, version 4.0 was performed. The association of HAE with survival was assessed in a landmark analysis. Logistic regression analysis was performed to predict HAE during the concomitant phase of chemotherapy.

Results HAE occurred in 36.4% and 28.6% of patients under CCNU/TMZ and TMZ treatment, respectively. The median onset of the first HAE was during concomitant chemotherapy (i.e. first CCNU/TMZ course or daily TMZ therapy), and 42.9% of patients with HAE receiving further courses experienced repeat HAE. Median HAE duration was similar between treatment arms (CCNU/TMZ 11.5; TMZ 13 days). Chemotherapy was more often discontinued due to HAE in CCNU/TMZ than in TMZ (19.7 vs. 6.3%, $p = 0.036$). The occurrence of HAE was not associated with survival differences ($p = 0.76$). Regression analysis confirmed older age (OR 1.08) and female sex (OR 2.47), but not treatment arm, as predictors of HAE.

Conclusion Older age and female sex are associated with higher incidence of HAE. Although occurrence of HAE was not associated with shorter survival, reliable prediction of patients at risk might be beneficial to allow optimal management of therapy and allocation of supportive measures.

Trial registration NCT01149109.

Keywords Glioblastoma · Temozolomide · Lomustine · MGMT · Hematotoxicity

Introduction

Glioblastoma is the most common malignant primary brain tumor in adults and has a detrimental prognosis despite standard-of-care treatment with surgery, radiotherapy, and temozolomide chemotherapy [1]. The presence of *O*^{6}*-methylguanine-DNA methyltransferase* (*MGMT*) promotor methylation defines a subgroup with prolonged survival and benefit from temozolomide (TMZ) [2]. CeTeG/NOA-09, a randomized phase III trial in patients with glioblastoma harboring a methylated *MGMT* promotor investigated a combination chemotherapy with TMZ and lomustine (CCNU) in addition to standard-of-care surgery and radiotherapy and was able to show an increase in median overall survival from 31.4 months to 48.1 months [3]. Within this trial, hematologic toxicity was more frequent in the combined treatment arm and fewer patients were able to complete all courses of chemotherapy, potentially leading to concerns regarding safety upon implementation of this therapy, while health-related quality of life was unaffected [4].

The aim of the present study is to provide a detailed analysis of patterns, predictors and prognostic effect of high

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grade hematologic adverse event (HAE) in the CeTeG/NOA-09 trial.

Methods

Study design, participants and treatment

The CeTeG/NOA-09 study design has been published previously [3]. Briefly, this German multicenter, randomized, open-label, phase III trial enrolled patients aged 18–70 years with newly diagnosed, histologically confirmed, chemotherapy-naïve, *MGMT* promotor methylated glioblastoma and a Karnofsky performance score of 70 or higher. Adequate hematological, hepatic, renal, and coagulation function and absence of medical treatment for any cancer were among inclusion criteria [3]. All patients provided written informed consent and the study was approved by the ethics committees of all participating centers. Patients were planned to receive standard focal radiotherapy (total 60 Gy) in addition to either standard oral TMZ (concomitant daily 75 mg/m^2, followed by six courses of 150–200 mg/m^2 for 5 days every 4 weeks) [5], or six 6-week courses of oral combined CCNU/TMZ (CCNU 100 mg/m^2 on day 1, TMZ 100–200 mg/m^2 on days 2–6) starting in the first week of radiotherapy. As described previously, dose modifications of CCNU/TMZ were performed according to results of mandatory weekly blood tests. If the nadir (white blood count < 1500 cells/µl or platelets < 50,000/µl) occurred after day 25, CCNU was reduced stepwise (steps in mg/m^2: 100, 75, 50, 0). TMZ dose was adapted according to the nadir during the first 25 days of the preceding course. Starting from 100 mg/m^2 in the first course, TMZ dose was increased to 120, 150, 200 mg/m^2 (maximum dose) in the next courses if no relevant hematotoxicity was observed. If the TMZ-related white blood count nadir was < 1500 cells/µl or platelet count < 50,000/µl, the TMZ dose of the next course was decreased by one step of the possible dose levels 200, 150, 120, 100, 75, 50, 0 mg/m^2 or decreased by two steps if white blood count was < 1000/µl or platelet count < 25,000/µl. If a course was delayed for more than 6 weeks, study therapy was discontinued. Non-hematological toxicity grade 3 or 4 led to discontinuation of the causing substance. All patients were followed up with clinical examination and MRI every 3 months.

HAE were defined as thrombopenia, leukopenia, lymphopenia, neutropenia, or anemia of grade 3 or higher. All adverse events were rated according to the Common Terminology of Clinical Adverse Events (CTCAE) version 4.0 and documented using pre-specified clinical reporting forms.

Statistical analysis

Standard descriptive statistics were used for all presented data. Group differences were analyzed with Fisher's exact test for categorical variables, and Mann-Whitney U test for continuous and ordinal variables as normal distribution could not be assumed.

Survival analysis was performed using Cox regression to analyze the impact of HAE and a delay of chemotherapy courses by 2–6 weeks. Given the time-dependent nature of HAE and delayed chemotherapy courses, i.e. an increasing cumulative incidence in patients receiving longer treatment, a landmark analysis was performed [6]. Three landmark times were specified: the end of the concomitant phase, 3rd and 6th chemotherapy course for the analysis of HAE, and the initiation of the 2nd, 4th and 6th course for the analysis of delay. Patients receiving chemotherapy until the respective landmark time were included, and the landmark datasets were stacked. Cox models were stratified by landmark times.

Uni- and multivariable logistic regression was performed to predict HAE during the concomitant phase of chemotherapy using previously published parameters [7, 8]. Significance level was set to alpha = 0.05 and all analyses were two-sided. Statistical calculations were carried out with SPSS (version 25, IBM Corp., Armonk, NY) and R (version 4.2, R core team 2022).

Results

Patterns of hematologic adverse events grade 3 or higher

The prevalence of HAE was higher in patients treated with CCNU/TMZ compared to treatment with TMZ alone without reaching statistical significance (36.4% (24 of 66) vs. 28.6% (18 of 63), respectively, p = 0.36) as reported before [3]. The median onset of a patient's first HAE was the concomitant phase of chemotherapy for both treatment arms (CCNU/TMZ: 1st course, interquartile range [IQR] 1–4, TMZ: conc. course, IQR: conc.–6th course, Fig. 1). In the concomitant phase of chemotherapy, HAEs occurred in 22.7% (15 of 66) of patients treated with CCNU/TMZ and 20.6% (13 of 63) patients treated with TMZ (p = 0.83).

The duration of HAE in the concomitant phase of chemotherapy was longer in the TMZ arm (concomitant: median 20 days, IQR 13–36.5, n = 13) compared to the CCNU/TMZ arm (1st course: median 10 days, IQR 2–24, n = 15) without reaching statistical significance (p = 0.10). We observed the opposite for HAE during adjuvant

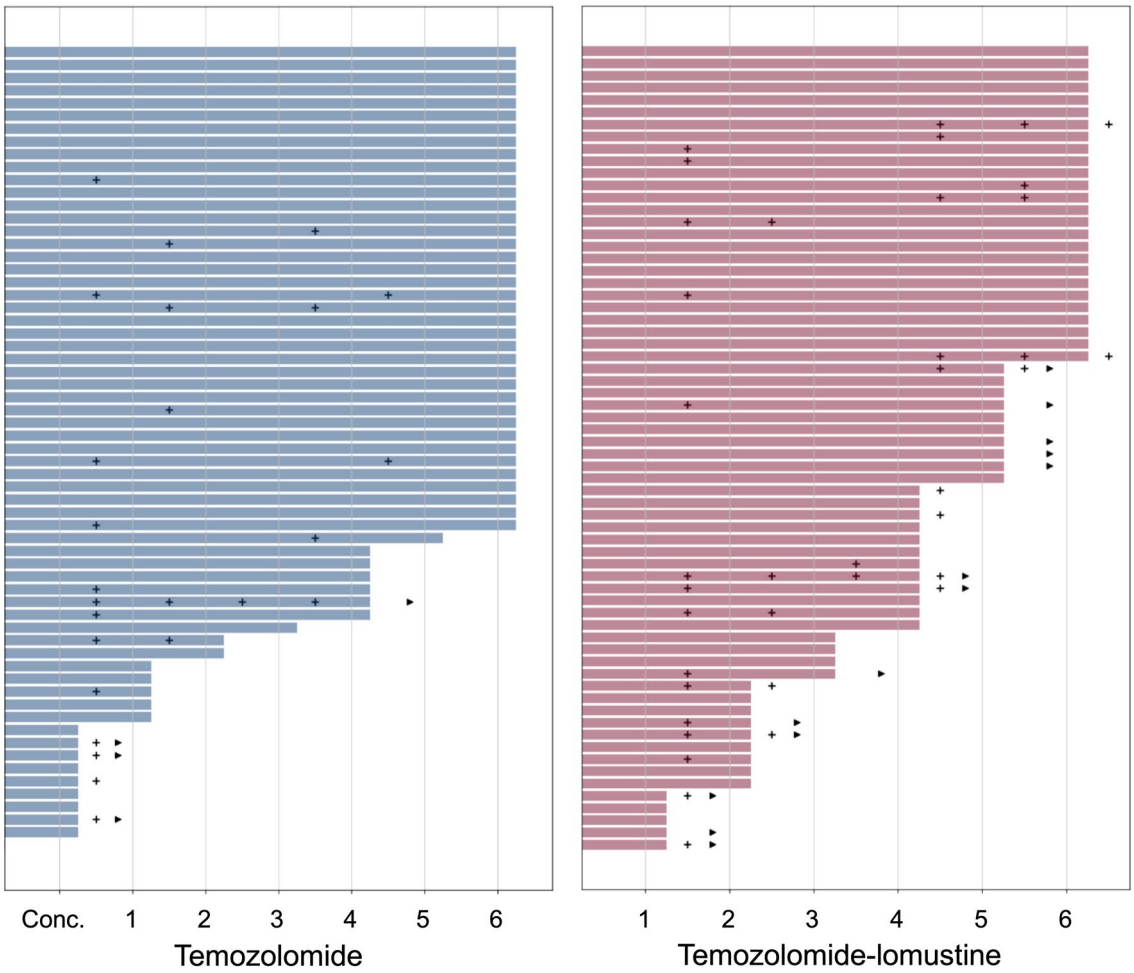

Fig. 1 Swimmer plot with individual patient data on applied chemotherapy courses and hematotoxicity. Crosses indicate hematological adverse events CTCAE grade 3 or 4, triangles indicate discontinuation of chemotherapy due to hematotoxicity or a resulting delay of more than 6 weeks. *conc*, *concomitant temozolomide*

courses; the median duration in TMZ was 6.5 days (IQR 4.5–13.25), compared to CCNU/TMZ with 20 days (IQR 11.25–51.5, p = 0.004). For all HAE episodes combined, the median duration was 11.5 days (IQR 5.25–22.75) in the CCNU/TMZ arm and 13 days (IQR 6.75–23.25) in the TMZ arm, respectively (p = 0.46). The duration of lymphopenia grade 3 or 4 was longer under CCNU/TMZ treatment, but this observation was based on a low number of cases (Table 1). No significant differences in duration were found for other HAEs (Table 1).

High risk neutropenia, defined as CTCAE grade 4 neutropenia > 7 days [9], occurred in 1 patient in the CCNU/TMZ arm, and no case of febrile neutropenia was recorded. No hematologic adverse event grade 5 occurred.

Table 1 Median duration and interquartile range (IQR) of hematotoxicity grade 3 or 4 episodes

	Lomustine-Temozolomide		Temozolomide		
	n (%)	Median duration (IQR)	n (%)	Median duration (IQR)	p
Leukopenia	10 (15.2)	9 (6 – 16)	8 (12.7)	9 (6–21)	0.76
Neutropenia	8 (12.1)	10.5 (8 – 14.75)	4 (6.3)	11 (5–21.5)	0.95
Thrombopenia	19 (28.8)	13 (4.25–20.5)	15 (23.8)	14.5 (5.5–31.75)	0.46
Lymphopenia	3 (4.5)	140 (90 – n.d.)	4 (6.3)	7 (6.5–21.5)	0.024
Anemia	1 (1.5)	2 (n.d. – n.d.)	3 (4.8)	12.5 (1 – n.d.)	0.99

Risk of recurring hematotoxicity

Among patients experiencing HAE, the median number of events was 1 (range, 1–4), with no difference between treatment arms (TMZ: 1 [range 1–4], CCNU/TMZ: 1 [range 1–4], p = 0.40). The risk of repeat HAEs during later courses among patients receiving at least one further course of chemotherapy after first HAE was 42.9% (15 of 35), numerically larger with CCNU/TMZ (47.6%, 10 of 21) compared to TMZ (35.7%, 5 of 14, p = 0.73).

Impact of hematotoxicity on chemotherapy and survival

Chemotherapy was completed (i.e. concomitant + 6 adjuvant courses of TMZ or 6 courses of CCNU/TMZ) in 40.6% (26 of 66) of patients receiving CCNU/TMZ and 59.4% (38 of 63) of patients receiving TMZ, as reported before [3]. Among patients receiving at least two courses of CCNU/TMZ or concomitant + first adjuvant course of TMZ, dose reductions were performed in 31.6% (36 of 114 patients); 36.1% (22 of 61) with CCNU/TMZ and 26.4% (14 of 53) with TMZ (p = 0.32).

According to protocol, chemotherapy was stopped if a course was delayed by more than 6 weeks. More patients stopped chemotherapy due to hematotoxicity or resulting delay under CCNU/TMZ (19.7%, 13 of 66) than TMZ (6.3%, 4 of 63, p = 0.0358, Fig. 1). The preceding hematotoxicity was grade 3 or 4 in all cases for TMZ but only in 53.8% of cases (7 of 13) for CCNU/TMZ, in the remaining cases lower grade hematotoxicity caused a delay of > 6 weeks. Chemotherapy was mostly stopped directly after the concomitant course of TMZ (75%, 3 of 4 patients) compared to later courses in CCNU/TMZ (first course: 20%, 3 of 15 patients).

The occurrence of HAE was not associated with shorter survival in the entire cohort (hazard ratio [HR] 1.06, 95% CI 0.73–1.54, p = 0.76) nor for both arms separately (TMZ: HR 1.08, 95% CI 0.63–1.85, p = 0.79, CCNU/TMZ: HR 1.03, 95% CI 0.61–1.75, p = 0.91).

Survival was also similar in patients with a delay of 2–6 weeks for any course of chemotherapy compared to patients without such a delay, both in the entire cohort (HR 0.70, 95% CI 0.43–1.16, p = 0.17) and for both arms separately (TMZ: HR 0.59, 95% CI 0.29–1.21, p = 0.15; CCNU/TMZ: HR 0.82, 95% CI 0.40–1.66, p = 0.58).

Prediction of hematotoxicity

In univariable logistic regression analysis, older age and female sex were associated with HAE (Table 2). Other previously published baseline parameters[7, 8], including reduced platelet counts, steroid or bowel medication and elevated creatinine had no predictive value for the occurrence of HAE. Analyzing either arms separately, no significant predictors were identified (Table 2). Multivariable analysis confirmed both female sex (odds ratio: 2.63, 95% CI 1.03–7.71, p = 0.043) and older age (odds ratio per year increment: 1.08, 95% CI 1.02–1.15, p = 0.01) as significant predictors for HAE.

Discussion

The present study provides a detailed comparative analysis of high grade hematotoxicity in the CeTeG/NOA-09 trial. No hematologic adverse event grade 5 was reported and the overall frequency of HAE showed a non-significant tendency to be higher with CCNU/TMZ as compared to TMZ [3]. Interestingly, the risk of HAE was highest during the first phase of chemotherapy (first course of CCNU/TMZ or concomitant TMZ, both during radiotherapy) with a similar frequency for both treatment arms, and the same number of patients in both arms discontinued therapy due to hematotoxicity as a consequence of the first phase of chemotherapy. The risk for repeat HAE during later courses was high

Table 2 Univariable logistic regression analysis identifies female sex and older age as predictors for hematotoxicity. Abbreviations: OR, odds ratio; CI, confidence interval; PPI, proton pump inhibitior treatment

	Pooled			Lomustine-Temozolomide			Temozolomide		
	OR	95% CI	P	OR	95% CI	p	OR	95% CI	p
Female sex	2.47	1.00–6.10	0.050	3.15	0.87–11.48	0.08	2.08	0.56–7.79	0.28
Age	1.08	1.02–1.15	0.011	1.09	0.99–1.19	0.06	1.08	0.99–1.18	0.09
Creatinine > 1 mg/dl	0.21	0.02–1.64	0.14	0.35	0.04–2.99	0.35	0.00	0–0	0.99
Platelets < 270/µl	0.37	0.27–1.62	0.37	0.77	0.22–2.69	0.68	0.56	0.15–2.11	0.39
PPI	0.69	0.24–2.02	0.50	0.67	0.14–3.64	0.67	0.58	0.16–2.79	0.67
Steroid treatment at baseline	1.01	0.26–3.87	0.99	2.5	0.40–15.56	0.33	0.42	0.48–3.72	0.44
Experimental arm	0.94	0.39–2.29	0.90	–	–	–	–	–	–

OR odds ratio, *CI* confidence interval, *PPI* proton pump inhibitior treatment

(42.9%) despite dose adjustment required by protocol, and affected patients should be monitored closely.

HAE patterns differed between the treatment arms: compared to TMZ, more patients developed HAE during later courses in the CCNU/TMZ arm. HAE in the TMZ arm lasted longest after concurrent treatment, while HAE from CCNU/TMZ were more prolonged during later courses. Most likely, the 6-week long exposure to TMZ during the concomitant phase of radiochemotherapy (employing > 1/3 of the total maximum temozolomide dose given during therapy) translates to a longer lasting nadir than the adjuvant 5/28 courses. On the other hand, CCNU/TMZ courses with increasing intensity of the CCNU/TMZ treatment scheme and potentially cumulative and prolonged toxicity of CCNU may explain the more frequent HAE onset in later courses. Consequently, more patients in the CCNU/TMZ arm compared to TMZ discontinued chemotherapy due to hematotoxicity or a resulting delay of > 6 weeks.

In line with previous reports, the occurrence of HAE was not associated with shorter survival in our analysis [10]. Nevertheless, the question is raised if secondary prophylactic measures enabling application of further courses in patients at risk of discontinuing therapy, e.g. romiplostim treatment after severe thrombopenia [11], might improve outcome.

The duration of HAE was similar between treatment arms with the exception of lymphopenia, which lasted longer in CCNU/TMZ than in TMZ. However, this observation was based on a small number of observations and lymphopenia is often perceived as a less threatening HAE due to the possibility of chemoprophylaxis for pneumocystis jirovecii pneumonia [12]. The overall low incidence of lymphopenia grade 3 or 4 in both treatment arms raises the possibility of underreporting of this specific HAE, as much higher frequencies of lymphopenia grade 3 or 4 have been reported in TMZ-treated glioblastoma patients [13].

Comparing HAE rates to former studies, one has to consider the different follow up schemes for blood tests. The present study required mandatory weekly blood tests to attribute hematotoxic events to the suspected causative chemotherapeutic drug and guide dose adjustment. This careful follow-up could explain the higher rate of HAE during standard TMZ treatment of 29%, compared to 16% upon monthly examination in the landmark EORTC 22981/26981-NCIC CE3 trial [5].

We also evaluated the prediction of hematotoxicity employing previously published baseline factors found to be predictive in glioma patients receiving TMZ chemotherapy [7, 8]. Logistic regression analysis confirmed the known higher risk among older and female patients [14], while treatment arm was not predictive. Analyzing treatment arms separately, no significant predictors were found, probably due to limited sample size and event rate. Although the analysis of health-related quality of life data showed no detrimental effect of CCNU/TMZ in the trial, adverse events should be minimized as much as possible, without reducing clinical efficacy [4].

The association of female gender and increased risk of HAE has been reported for temozolomide in glioma treatment [7, 14, 15], but also for other chemotherapeutics agents employed in a variety of cancers [16]. Indeed, sex differences in pharmacologic response and adverse drug reactions are increasingly observed and female sex is associated with a greater risk of adverse events [17]. These observations are attributed to differences in pharmacokinetics and pharmacodynamics [18]. Females have a higher percentage of body fat, affecting distribution volumes, but obesity and body fat content were not correlated with myelosuppression [14]. Other potential mechanisms underlying the sex-dependently increased HAE risk include a lower glomerular filtration rate and activity of hepatic enzymes and drug transporters, which may affect drug clearance [16, 17]. While these aspects demand further investigation, recommended dose adjustments and monitoring for HAE in female and elderly patients carrying the highest risk for HAE seems paramount [3].

In addition to clinical factors, little is known about the contribution of genetic factors to hematotoxicity susceptibility. Lombardi et al. found a methylated *MGMT* promoter in blood cells of patients with severe hematologic toxicity [8], and single nucleotide polymorphisms of *MGMT* are under observation [19]. Prospective evaluation of these factors in larger series is needed to better understand the molecular basis of hematotoxicity.

Conclusion

This detailed analysis of HAE in the CeTeG/NOA-09 trial supports the clinical follow-up and management of patients treated with CCNU/TMZ or TMZ. We conclude that close monitoring is mandatory, and potentially supportive measures might be helpful. Importantly, HAE was not associated with shorter survival. Increased HAE risk in older and female patients was confirmed, but reliable prediction of HAE should be further examined in larger studies.

Author contribution JW, CS and UH designed the analysis. JW performed data analysis and wrote the first draft of the manuscript. CS and UH supervised the work. All authors contributed to data acquisition, commented on previous versions and read and approved the final manuscript.

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Data availability The dataset is available from the corresponding author upon reasonable request. The data are not publicly available due to privacy restrictions.

Declarations

Conflict of interest UH has received lecture and/or advisory board honoraria from Medac, Novartis, Daichii-Sankyo, Noxxon, AbbVie, Bayer, Janssen, and Karyopharm. CS has received lecture or advisory board honoraria from AbbVie, Bristol-Myers Squibb, HRA Pharma, Medac, Roche, and Seagen. GT has received lecture, consultant or advisory board honoraria from AbbVie, Bayer, Boehringer Ingelheim, Medac, Novartis, Novocure) and research grants from Roche Diagnostics and Medac. JS has received lecture and/or advisory board honoraria or travel cost reimbursement from Abbvie, Medac, Med-Update, Roche, Novocure and Seagen. MGs reports personal fees from Roche, Novartis, Daichi Sankyo, Novocure, Bayer, frm Janssen-Cillag, Merck, Kyowa Kirin, Seagen, and grants from Novocure. FSG reports advisory board honoraria from Novocure. GT has served on advisory boards of AbbVie, Bayer, Boehringer Ingelheim, received consulting fees from AbbVie, Bayer; received speaker fees from Medac and Novocure. FR has received lecture and/or consulting honoraria from Stryker, Brainlab, Spineart, Icotec, royalties from Spineart and research support from Icotec. The other authors declare they have no financial interests.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the Helsinki Declaration and its later amendments and the Guidelines for Good Clinical Practice. The study was approved by the Ethics committees of all participating centers.

Informed to consent Written informed consent was obtained from all individual participants included in the study.

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