Neuro-Oncology
24(11), 2001–2004, 2022 | https://doi.org/10.1093/neuonc/noac172 | Advance Access date 30 July 2022

Letter to the Editor

Improved seizure control in patients with recurrent glioblastoma treated with bevacizumab

Seizures are a frequent symptom in patients with glioblastoma and bear a relevant impact on quality of life.[1–3] Retrospective studies have indicated that temozolomide may improve seizure control in glioma patients.[2,4] Bevacizumab, an approved treatment for recurrent glioblastoma,[3] may also decrease seizure frequency, eg, by reducing edema, with potential implications for quality of life. Bevacizumab was approved in Switzerland in 2009 and epidemiological data showed that bevacizumab use increased in the Canton of Zurich in the years 2010-2014.[5]

Here, we retrospectively reviewed the electronic charts of glioblastoma patients at first recurrence treated either with (N = 55) or without (N = 61) a bevacizumab-containing regimen. Patients were diagnosed with glioblastoma[6] between 2010 and 2014 in the Canton of Zurich and were treated at the University Hospital Zurich. Occurrences and dynamics of seizures before and after first recurrence were assessed. Categorical and continuous variables were compared by the chi-square and the Mann-Whitney *U* test, respectively. Associations of clinical parameters and seizures were analyzed by binary logistic regression. This study was approved by the local ethics committee (KEK-ZH-Nr. 2015-0437).

The results are summarized in Table 1. Patients in the bevacizumab group were younger and the O^6-methylguanine DNA methyltransferase (*MGMT*) promoter was less frequently methylated in tumors in the bevacizumab group. At first recurrence, most patients in the bevacizumab group received bevacizumab alone (N = 43, 78.2%), followed by a combination treatment of surgery and bevacizumab (N = 6, 10.9%). Patients in the control group mainly received alkylating chemotherapy alone (N = 27, 44.3%) or surgery plus chemotherapy (N = 14, 23%) or radiotherapy alone (N = 12, 19.7%). Patients who received bevacizumab at the time of first recurrence had inferior overall survival (OS) (17.3 months vs 18.8 months, $P = .009$) and post-recurrence survival (PRS) (7.3 months vs 9.9 months, $P = .015$) than patients in the control group.

Fifteen patients (28.8%) in the bevacizumab group and 27 patients (45.8%) in the control group had suffered from seizures within the 12 weeks preceding the first tumor recurrence. Within 3 months after initiation of second-line treatment, 4 patients (7.7%) in the bevacizumab group experienced further seizures whereas 23 patients (39.0%) in the control group still suffered from seizures ($P < .001$). Four patients in the group of the 23 patients who had surgery at the time of first recurrence had a seizure within the 12-week period after recurrence (bevacizumab group N = 0, control group N = 4). An early postoperative seizure (≤21 days after surgery) was seen in one patient only. In the overall cohort, 37 patients had not experienced seizures until their first recurrence (bevacizumab group N = 17, 31.5%; control group N = 20, 33.9%; $P = .784$), of which only 7 patients (18.9%) experienced a seizure in the 12 weeks after recurrence (bevacizumab group N = 3, control group N = 4). Multivariable binary logistic regression analyses, including age, sex, performance status, extent of resection, *MGMT* promoter methylation status, and first-line treatment confirmed bevacizumab to be inversely associated with seizures in the 12 weeks after first recurrence (odds ratio [OR] 0.23, 95% confidence interval [CI] 0.06-0.94, $P = .009$).

Moreover, an augmentation of the anti-epileptic treatment, either by increase in dose or addition of another substance, was observed for only 6 patients (14.3%) in the bevacizumab group compared to 24 patients (52.2%) in the control group ($P = .002$).

Limitations of this study arise from its retrospective nature, raising the possibility of an underestimation of seizure frequencies and the small sample size. Prospective studies should seek to include established quality of life measures, as well as structured assessments for seizures. Nevertheless, this study shows that bevacizumab may contribute to a reduction in seizure frequency in patients with recurrent glioblastoma and therefore supporting clinical benefit and increased quality of life in patients not qualifying for further tumor-specific treatments.

Funding

This work was supported by personal grants ("Filling the gap") from the University of Zurich, Switzerland to C.H., K.S., and D.G. and by a personal grant from the "Walter und Gertrud Siegenthaler Stiftung" to K.S.

Conflict of interest statement. E.L.R. has received a research grant from BMS and personal fees from Adastra, Bayer, Janssen, Leo Pharma, Pierre Fabre, and Seattle Genetics. P.R. has received honoraria for lectures or advisory board participation from Bristol-Myers Squibb, Boehringer Ingelheim, Debiopharm, Merck Sharp & Dohme, Novocure, QED, and Roche and research support from Merck Sharp & Dohme and Novocure. M.W. has received research grants from Merck Sharp & Dohme (MSD), Merck (EMD), Novocure, and Quercis, and honoraria for lectures or advisory board participation or consulting from Bristol Meyer Squibb (BMS), Medac, Merck Sharp & Dohme (MSD), Merck (EMD), Nerviano Medical Sciences, Novartis, Orbus, Philogen, Roche, and Y-mAbs Therapeutics. All remaining authors declare that they have no conflict of interest.

Table 1. Patient Characteristics, Survival, Seizure Patterns, and Binary Logistic Regression Analyses for Association of Bevacizumab Use With Seizure Occurrence After First Recurrence

		Bevacizumab (N = 55)		Control Group (N = 61)		*P*-value
		N	%	N	%	
Patient characteristics						
Age (years)	Median	54.0		60.0		.038
Sex	Female	19	34.5	19	31.1	.697
	Male	36	65.5	42	68.9	
KPS at diagnosis	<70	8	14.5	4	6.6	.227
	70-80	37	67.3	40	65.6	
	90-100	10	18.2	17	27.9	
Extent of resection	Biopsy	13	23.6	7	11.5	.223
	Partial resection	21	38.2	27	44.3	
	Gross total resection	21	38.2	27	44.3	
MGMT promoter methylation status	Methylated	9	26.5	24	63.2	.008
	Unmethylated	25	73.5	14	36.8	
	No data	21	–	23	–	
First-line treatment	Chemotherapy alone	4	7.3	11	18.0	.012
	RT alone	4	7.3	13	21.3	
	RT plus TMZ	43	78.2	30	49.2	
	Other[a]	4	7.3	7	11.5	
Second-line treatment	Bevacizumab alone	43	78.2			<.001
	Bevacizumab plus chemotherapy	3	5.5	–	–	
	Bevacizumab plus other[b]	3	5.5	–	–	
	Resection followed by bevacizumab	6	10.9	–	–	
	Chemotherapy alone	–	–	27	44.3	
	Resection alone	–	–	2	3.3	
	Resection followed by chemotherapy	–	–	14	23.0	
	RT alone	–	–	12	19.7	
	Resection followed by RT	–	–	1	1.6	
	Other[c]	–	–	5	8.2	
Survival						
Median follow-up (months)		16.6		18.2		.118
PFS events, N		55		61		
Median PFS (months, 95% CI)		5.8 (5.0-6.7)		6.4 (5.2-7.6)		.042
PRS events, N		54		56		
Median PRS (months, 95% CI)		7.3 (5.9-8.8)		9.9 (8.1-11.4)		.015
OS events, N		51		51		
Median OS (months, 95% CI)		17.3 (14.6-20.0)		18.8 (17.1-20.4)		.009
Alive at last follow-up, N		4 (7.3%)		10 (16.4%)		
Seizure patterns						
		N	%	N	%	
Seizures (at diagnosis)	Yes	32	59.3	33	54.2	.721
	No seizure	22	40.7	26	39.0	
	No data	1	–	2	–	
Seizures until first progression	Yes	37	68.5	39	66.1	.784
	No seizure	17	31.5	20	33.9	
	No data	1	–	2	–	

Table 1. Continued

		Bevacizumab (N = 55)		Control Group (N = 61)		*P*-value
		N	%	N	%	
Seizures (any time during course of the disease)	Yes	40	72.7	43	70.5	.790
	No	15	27.3	18	29.5	
Seizures (12 weeks preceding tumor recurrence)	Yes	15	28.8	27	45.8	.067
	No	37	71.2	32	54.2	
	No data	3	–	2	–	
Seizure type (12 weeks preceding tumor recurrence)	Focal aware	11	73.3	12	44.4	.081
	Focal impaired awareness	0	–	7	25.9	
	Generalized	1	6.7	4	14.8	
	Focal and generalized	0	–	1	3.7	
	Status epilepticus	3	20.0	3	11.1	
Seizures (12 weeks after recurrence)	Yes	4	7.7	23	39.0	<.001
	No	48	92.3	36	61.0	
	No data	3	–	2	–	
Seizure type (12 weeks after recurrence)	Focal aware	2	50.0	13	56.5	.440
	Focal impaired awareness	0	–	4	17.4	
	Generalized	1	25.0	5	21.7	
	Status epilepticus	1	25.0	1	4.3	
Seizures (12 weeks after recurrence)[d]	Yes	3	7.1	23	40.3	<.001
	No	39	92.9	34	59.7	
	Excluded patients	13	–	4	–	
AED change[e] (12 weeks prior to 12 weeks post first recurrence)	Stable	33	78.6	19	41.3	.002
	Increased	6	14.3	24	52.2	
	Decreased	3	7.1	3	6.5	
	no AED	13	–	15	–	
Binary logistic regression analyses						
Parameter		Odds ratio for seizure occurrence		95% CI		*P*-value
Univariable N = 111						
Bevacizumab: yes vs no (ref)		0.13		0.04-0.41		<.001
Multivariable (data for N = 70 patients with all covariables available):						
Bevacizumab: yes vs no (ref)		0.23		0.06-0.94		.009
Sex: female vs male (ref)		2.98		0.83-10.70		.095
Age: ≤65 years vs >65 years (ref)		3.28		0.67-16.20		.144
KPS: ≤70% vs >70% (ref)		0.74		0.21-2.56		.629
Extent of resection: biopsy/partial vs gross total resection (ref)		0.76		0.22-2.60		.656
MGMT promoter methylation: methylated vs unmethylated (ref)		0.99		0.27-3.61		.986
First-line treatment: RT or CT alone or others[f] vs RT plus TMZ (ref)		2.85		0.63-12.85		.173

Abbreviations: AED, anti-epileptic drug; CI, confidence interval; CT, chemotherapy; KPS, Karnofsky performance status; MGMT, O^6-methylguanine DNA methyltransferase; N, number; OS, overall survival; PFS, progression-free survival; PRS, post-recurrence survival; ref, reference; RT, radiotherapy; TMZ, temzolomide.

[a]Bevacizumab group: N = 1 RT plus TMZ plus cilengitide, N = 2 RT plus TMZ plus tumor treating fields, N = 1 RT plus TMZ plus rindopepimut/placebo; control group: N = 2 RT plus temsirolimus, N = 2 RT plus TMZ plus tumor treating fields, N = 3 RT plus TMZ plus rindopepimut/placebo.

[b]N = 1 tumor-treating fields, N = 1 RT, N = 1 experimental drug (antiplacental growth factor monoclonal antibody).

[c]N = 3 immune checkpoint inhibitors, N = 1 parvovirus treatment, N = 1 chemotherapy plus ABT-414.

[d]Excluding N = 12 patients who died within 12 weeks after first recurrence, and N = 5 patients with missing data.

[e]Any augmentation in anti-epileptic medication monotherapy and/or addition of a further anti-epileptic treatment was considered an increase; any dose reduction of an anti-epileptic medication and/or omission of a medication was considered a decrease.

[f]N = 1 RT plus TMZ plus cilengitide, N = 2 RT plus TMZ plus tumor treating fields, N = 2 RT plus TMZ plus rindopepimut/placebo; N = 2 RT plus temsirolimus.

Authorship statement. Study conception and design: C.H., M.W., and D.G. Material preparation, data collection, and analysis: C.H., D.G., and K.S. Writing the first draft of the manuscript: C.H., M.W., and D.G. Critical input and review of the manuscript: all authors. Approval of the final manuscript: all authors.

Caroline Hertler, Katharina Seystahl, Emilie Le Rhun, Hans-Georg Wirsching, Patrick Roth, Michael Weller, and Dorothee Gramatzki

Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland (C.H., K.S., E.L.R., H.-G.W., P.R., M.W., D.G.); Competence Center for Palliative Care, University Hospital Zurich, Zurich, Switzerland (C.H.); Department of Neurosurgery, Clinical Neuroscience Center, University Hospital and University of Zurich, Zurich, Switzerland (E.L.R.)

Corresponding Author: Dorothee Gramatzki, MD, Department of Neurology, Clinical Neuroscience Center, University Hospital and University of Zurich, Frauenklinikstrasse 26, 8091 Zurich, Switzerland (dorothee.gramatzki@usz.ch).

References

1. Mastall M, Wolpert F, Gramatzki D, et al. Survival of brain tumour patients with epilepsy. *Brain.* 2021;144(11):3322–3327.
2. Koekkoek JA, Kerkhof M, Dirven L, et al. Seizure outcome after radiotherapy and chemotherapy in low-grade glioma patients: a systematic review. *Neuro Oncol.* 2015;17(7):924–934.
3. Wen PY, Weller M, Lee EQ, et al. Glioblastoma in adults: a Society for Neuro-Oncology (SNO) and European Society of Neuro-Oncology (EANO) consensus review on current management and future directions. *Neuro Oncol.* 2020;22(8):1073–1113.
4. Climans SA, Brandes AA, Cairncross JG, et al. Temozolomide and seizure outcomes in a randomized clinical trial of elderly glioblastoma patients. *J Neurooncol.* 2020;149(1):65–71.
5. Gramatzki D, Roth P, Rushing EJ, et al. Bevacizumab may improve quality of life, but not overall survival in glioblastoma: an epidemiological study. *Ann Oncol.* 2018;29(6):1431–1436.
6. Louis DN, Perry A, Wesseling P, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. *Neuro Oncol.* 2021;23(8):1231–1251.