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Abstract: The integrin antagonist cilengitide has been explored as an adjunct with anti-angiogenic properties to standard of care temozolomide chemoradiotherapy (TMZ/RT → TMZ) in newly diagnosed glioblastoma. Preclinical data as well as anecdotal clinical observations indicate that anti-angiogenic treatment may result in altered patterns of tumor progression. Using a standardized approach, we analyzed patterns of progression on MRI in 21 patients enrolled onto a phase 2 trial of cilengitide added to TMZ/RT → TMZ in newly diagnosed glioblastoma. Thirty patients from the experimental treatment arm of the EORTC/NCIC pivotal TMZ trial served as a reference. MRIcro software was used to map location and extent of initial preoperative and recurrent tumors on MRI of both groups into the same stereotaxic space which were then analyzed using an automated tool of image analysis. Clinical and outcome data of the cilengitide-treated patients were similar to those of the EORTC/NCIC trial except for a higher proportion of patients with a methylated O(6)-methylguanyl-DNA-methyltransferase gene promoter. Analysis of recurrence pattern revealed neither a difference in the size of the recurrent tumor nor in the distance of the recurrences from the preoperative tumor location between groups. Overall frequencies of distant recurrences were 20 % in the reference group and 19 % (4/21 patients) in the cilengitide group. Compared with TMZ/RT → TMZ alone, the addition of cilengitide does not alter patterns of progression. This analysis does not support concerns that integrin antagonism by cilengitide may induce a more aggressive phenotype at progression, but also provides no evidence for an anti-invasive activity of cilengitide in patients with newly diagnosed glioblastoma.

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Cilengitide treatment of newly diagnosed glioblastoma patients does not alter patterns of progression

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Abstract

The integrin antagonist cilengitide has been explored as an adjunct with anti-angiogenic properties to standard of care temozolomide chemoradiotherapy (TMZ/RT→TMZ) in newly diagnosed glioblastoma. Preclinical data as well as anecdotal clinical observations indicate that anti-angiogenic treatment may result in altered patterns of tumor progression. Using a standardized approach, we analyzed patterns of progression on MRI in 21 patients enrolled onto a phase 2 trial of cilengitide added to TMZ/RT→TMZ in newly diagnosed glioblastoma. Thirty patients from the experimental treatment arm of the EORTC/NCIC pivotal TMZ trial served as a reference. MRIcro software was used to map location and extent of initial preoperative and recurrent tumors on MRI of both groups into the same stereotaxic space which were then analyzed using an automated tool of image analysis. Clinical and outcome data of the cilengitide-treated patients were similar to those of the EORTC NCIC trial except for a higher proportion of patients with a methylated O^6-methylguanyl-DNA-methyltransferase (*MGMT*) gene promoter. Analysis of recurrence pattern revealed neither a difference in the size of the recurrent tumor nor in the distance of the recurrences from the preoperative tumor location between groups. Overall frequencies of distant recurrences were 20% in the reference group and 19% (4/21 patients) in the cilengitide group. Compared with TMZ/RT→TMZ alone, the addition of cilengitide does not alter patterns of progression. This analysis does not support concerns that integrin antagonism by cilengitide may induce a more aggressive phenotype at progression, but also provides no evidence for an anti-invasive activity of cilengitide in patients with newly diagnosed glioblastoma.

Key words: glioblastoma; integrins; cilengitide; relapse pattern; MRIcro

Introduction

Most current efforts to improve the outcome for patients with newly diagnosed glioblastoma focus on the addition of anti-angiogenic agents to the standard of care of concomitant chemoradiotherapy with temozolomide (TMZ/RT→TMZ) [1]. The majority of pharmacological approaches focus on inhibition of the vascular endothelial growth factor (VEGF) pathway, but additional targets are being explored, notably integrins. Preclinical data obtained in rodent glioma models suggest that VEGF antagonism may induce a more infiltrative, disseminated phenotype of gliomas [2,3]. No such animal data are available for integrin antagonism.

We have previously developed an analysis tool to explore whether comparable groups of patients differ in their patterns of progression. This tool was first used for analysis of the pivotal EORTC/NCIC TMZ trial; and allowed to falsify the hypothesis that the addition of TMZ to RT alters the pattern of progression of glioblastomas [4]. Similarly, using this tool we did not confirm the notion that bevacizumab therapy alters tumor biology to a more invasive phenotype [5]. In the present study, we asked whether patients treated with the integrin antagonist cilengitide would exhibit an altered pattern of progression.

Patients and methods

We retrieved the matched pre- and post-operative MRI scans as well as the MRI scan documenting progression of patients enrolled into a single-arm phase 2 clinical trial of cilengitide plus TMZ/RT→TMZ in newly diagnosed glioblastoma [6]. Thirty patients from the experimental treatment arm of the EORTC/NCIC 26981/22981 National Cancer Institute of Canada (NCIC) CE.3 trial served as a reference [1,4]. From these patients MRI scans at baseline and progression were available for a retrospective recurrence pattern analysis [4]. Patterns of progression were analyzed as described hereib; in brief, brain lesions were demonstrated by contrast-enhanced T_1-weighted MRI sequences. The MR scans were oriented along the bicommissural plane. Mapping of lesions was performed blinded to the clinical features of the patients. The boundaries of the tumor location at baseline and at follow-up were delineated using MRIcro software [7] and mapped on the T_1-template MRI from the Montreal Neurological Institute (www.bic.mni.mcgill.ca/cgi/icbm_view) that is distributed with MRIcro. Tumors were mapped for each individual patient, with separate tumor maps generated for both the baseline and recurrence scan. By transforming each individual brain and lesion into the same stereotaxic space, the procedure allowed us to superimpose lesions of different individuals to find regions of mutual involvement and conduct subtraction analysis. These techniques are well established in stroke research and have been applied to brain tumor patients before [4,5].

Further, by using MRIcro, tumor volume and the location of the center-of-mass of the tumor for each individual were computed. The center-of-mass is the mean position for all tumor-affected voxels in each of the three spatial dimensions, resulting in a single cartesian coordinate (X,Y,Z position). In the case of a single spherical tumor, the center-of-mass thus will be located right in its center, while with, e.g. a U-shaped

configuration the center-of-mass may lie outside the tumor itself. Likewise this measure is influenced by satellites of the main tumor mass and thus sensitive to the development of satellites between baseline and recurrent images.

For an additional case-by-case analysis a distant recurrence on T1 contrast-enhanced (T_{1+c}) sequences was defined as one of the following: a) qualitative assessment of well-defined recurrence centered outside a 2 cm margin around the outer border of the primary site or margin of the resection cavity or a shift of the center-of-mass by more than half of the diameter of the pretreatment tumor, b) new tumor satellites, c) new involvement of the contralateral hemisphere [4]. Only patients with progressive disease (PD) as the reason for failure of therapy were included. Analysis was done blinded to treatment in the reference or cilengitide group on contrast-enhanced T_1-weighted images in the axial plane. The boundary of the tumor location at baseline and at follow-up was delineated using OsiriX software (Softonic, Stanford, CA, USA).

A two-tailed t-test was conducted to determine if the two treatments influenced the size of recurrent tumors or the distance of the center-of-mass between the baseline and follow-up scan or both. A sample size of 20 per group would be sufficient to detect a 35% difference for the movement of the center-of-mass with a power of 70% that would be regarded clinically relevant.

Median progression-free and overall survival for the cilengitide group were calculated by Kaplan-Meier survival analysis using SPSS software version 21 for Windows (IBM, Armonk, NY, USA).

Results

For 21 representative patients (21/53, 40%) treated prospectively within the cilengitide added to standard TMZ/RT→TMZ 010 pilot phase II protocol complete digitized imaging was available for review and analysis [6]. The reference group included all 30 patients with sufficient MRI information from the experimental arm of the EORTC 26981/22981 NCIC CE.3 trial, as previously reported [1,4]. Table 1 summarizes characteristics of the patients, tumors and outcome of the two cohorts. Overall, patient characteristics appear comparable, with the exception of a higher proportion of patients with an unknown *MGMT* methylation status in the historical reference cohort (23% vs 14%). Patients in both groups did not differ with respect to extent of resection. The median time between imaging used for the baseline MRI scanning and first histological diagnosis was 0.2 months in both groups. The median time between baseline MRI and the MRI demonstrating recurrence was 7.3 months in the reference group and 9.0 months in the cilengitide group, comparable to the whole study cohort.

To identify any preferential directions of tumor growth or of tumor shrinkage in either group, the tumor locations at baseline were subtracted from the superimposed tumor locations after treatment in each treatment group. For both treatment groups, we found no marked anatomical shift of tumor locations after treatment. The overlap frequencies after substraction did not exceed 35% of overlap at any location indicating that the anatomical differences between baseline and follow-up measurement were small and not directionally specific.

Recurrent tumors volumes (measured in voxels on a per-patient basis) were 1.29-fold (±0.37) and 1.4-fold (±0.41) larger than the initial tumors in the reference group and in the cilengitide group, respectively (p=0.51)

For the center-of-mass measure, the distance between baseline and follow-up centroids was computed for each individual, providing a measure of excentricity or a large shift in location, e.g., when a new satellite tumor has developed. The movement of the center-of-mass between the baseline and follow-up scan in the reference cohort and the cilengitide cohort revealed no difference with a mean movement of 12.03 mm (±0.39) for the reference group and 13.22 mm (±0.60) for the cilengitide treated patients (p=0.53). The case-by-case comparison suggested the same conclusion: the frequency of distant recurrences was 18% in the reference and 19% in the cilengitide group (Chi^2=0.92, p=0.12).

Discussion

The patterns of progression in glioblastoma have recently attracted a lot of interest, both because of preclinical data and clinical observations that suggested a specific change in the pattern of progression depending on treatment, i.e. radiotherapy, TMZ chemotherapy or novel anti-angiogenic treatments [8,9,3,10,2]. Using a previously established and standardized tool and radiological software we compared the pattern of progression of 21 patients who were prospectively treated with cilengitide in addition to standard TMZ/RT→TMZ with 30 reference patients who received standard chemoradiotherapy alone in a previous clinical trial. In contrast to the initial hypothesis, we did not demonstrate a difference in invasion pattern or location of tumor recurrence (e.g. farther distance from the initial tumor location) for the patients having been treated with cilengitide. Interestingly, one patient from the cilengitide group who experienced a local recurrence intracranially was diagnosed with histologically proven pulmonary metastasis in the course of the disease. However, this case is exceptional and no further patients with systemic metastasis were described in this trial [6].

Similar to cilengitide and despite strong preclinical evidence of development of a more aggressive phenotype and increased invasion after treatment with bevacizumab [2,3,10], a recent analysis of the imaging data of patients treated in the AVAGlio trial (bevacizumab added to TMZ/RT—TMZ) did not indicate a clinically relevant change in invasion pattern or tumor phenotype in bevacizumab-treated patients [11]. Yet, it is noteworthy that RTOG-0825, a similar trial, reported impaired quality of life and decreased scores on some tests of cognitive function in bevacizumab-treated patients, although no such data were reported by the AVAGlio investigators [11,12]. Careful comparison of both data sets including neuroimaging

will be necessary to better understand these conflicting data and a possible role of neuroimaging changes.

While preclinical evidence suggested anti-invasive properties of TMZ, or potentially promotion of invasive escape mechanisms after irradiation, or after VEGF inhibition, systematic analyses of the pattern of treatment failure does not substantiate these findings in the clinical setting. Although all analyses were conducted on relatively small subsets of patients, the consistency of the finding raises questions to whether the preclinical models reflect the human situation adequately.

This is the first analysis ever of a potential modulation of patterns of progression by the novel class of compounds of integrin inhibitors. The observation that no change in the patterns of progression in a cohort of cilengitide-treated patients compared to a cohort of patients from the experimental arm of the EORTC 26981/22981 NCIC CE.3 was observed is reassuring. The major limitation of the present study is the small sample size and the uncertainty of its relevance in the future: preliminary results from the subsequently performed phase 3 trial, CENTRIC, indicate that the primary endpoint of prolonging overall survival was not reached [13]. Yet, our analysis serves as a baseline and reference for the future study of the role of modulation of integrins in the treatment of newly diagnosed glioblastoma.

Conflict of interest statement

The following authors disclose financial relationship with Merck KGaA (Darmstadt, Germany): Bart Neyns (research funding), Michael Weller (research funding and advisory role), Paul M Clément (payment for invited lectures and consultancy), Roger Stupp (consultancy), Jörg Tonn (advisory role and honoraria), Martin Picard (employment).

Günter Eisele, Antje Wick, Anna-Carina Eisele, Ghazaleh Tabatabai, Dietmar Krex, Matthias Simon, Uwe Schlegel, Adrian Ochsenbein, Guido Nikkhah and Wolfgang Wick have no conflicts of interest to disclose.

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Table Patient characteristics

	MRI study cohort from [6] (n=21)		Complete study cohort from [6] (n=52)		Reference cohort from EORTC 26981-22981 NCIC CE3 [1,4] (n=30)	
Patient characteristics	No. of patients	%	No. of patients	%	No. of patients	%
Age, years						
Median	53		57		56	
Range	32-67		32-68		36-66	
Sex						
Male	11	52	32	62	18	60
Female	10	48	20	38	12	40
ECOG performance status					KPS*	
0 or 1	20	95	48	92	90-100: n=18	60
2	1	5	4	8	70-80: n=12	40
Prior treatment						
Corticosteroids	19	90	43	83	23	77
Debulking surgery	18	86	43	83	18	60
Complete resection	9	43	23	44	n/a	
Partial resection	9	43	20	39	n/a	
Biopsy	3	14	9	17	12	
MGMT promoter status						
Methylated	9	43	23	44	10	33
Unmethylated	9	43	22	42	13	43
Unknown	3	14	7	13	7	23
Median PFS (months, 95% CI)	8.1 (6.4-9.8)		8.0 (6.0-10.7)		7.1 (5.8-8.2)	
Median OS (months, 95% CI)	15.7 (11.2-20.1)**		16.1 (13.1-23.2)		14.4 (13.4-16.8)	

*Eastern cooperative oncology group (ECOG) measure 0 = KPS 100; ECOG 1 = KPS 80 to 90; ECOG 2 = KPS 60 to 70, according to [13]. KPS: Karnofsky Performance Status. CI: confidence interval. n/a: information not available. PFS: progression-free survival. OS: overall survival.

**5 patients censored