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Advantages of high *b*-value diffusion-weighted imaging to diagnose pseudo-responses in patients with recurrent glioma after bevacizumab treatment

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ABSTRACT

Background: The diagnosis of pseudo-responses after bevacizumab treatment is difficult. Because diffusion-weighted imaging (DWI) is associated with cell density, it may facilitate the differentiation between true- and pseudo-responses. Furthermore, as high *b*-value DWI is even more sensitive to diffusion, it has been reported to be diagnostically useful in various clinical settings.
Materials and methods: Between September 2008 and May 2011, 10 patients (5 males, 5 females; age range 6–65 years) with recurrent glioma were treated with bevacizumab. All underwent pre- and post-treatment MRI including T2- or FLAIR imaging, post-gadolinium contrast T1-weighted imaging, and DWI with *b*-1000 and *b*-4000. Response rates were evaluated by MacDonald- and by response assessment in neuro-oncology working group (RANO) criteria. We also assessed the response rate by calculating the size of high intensity areas using high *b*-value diffusion-weighted criteria. Prognostic factors were evaluated using Kaplan–Meier survival curves (log-rank test).
Results: It was easier to identify pseudo-responses with RANO- than MacDonald criteria, however the reduction of edema by bevacizumab rendered the early diagnosis of tumor progression difficult by RANO criteria. In some patients with recurrent glioma treated with bevacizumab, high *b*-value diffusion-weighted criteria did, while MacDonald- and RANO criteria did not identify pseudo-responses at an early point after the start of therapy.
Discussion and conclusion: High *b*-value DWI reflects cell density more accurately than regular *b*-value DWI. Our findings suggest that in patients with recurrent glioma, high *b*-value diffusion-weighted criteria are useful for the differentiation between pseudo- and true responses to treatment with bevacizumab.

1. Introduction

Glioblastoma is the most common malignant primary neoplasm of the central nervous system. Despite aggressive treatment, it almost always recurs with fatal consequences. As vascular endothelial growth factor (VEGF) and its receptors are highly expressed in glioblastoma, VEGF may constitute an important molecular target in its treatment. VEGF increases vascular permeability and contributes to contrast enhancement and the peritumoral edema associated with these tumors. Anti-angiogenic agents, especially those targeting VEGF such as bevacizumab, can significantly reduce vascular permeability. This results in diminution of the enhanced lesion irrespective of changes in the tumor size. Therefore, it is very difficult to determine the responder status of glioma patients treated with bevacizumab on conventional MR images and some tumors thought to have responded to bevacizumab therapy exhibit progression without manifesting an increase in the size of the gadolinium-enhanced tumor. This phenomenon, defined as a "pseudo-response", has been observed immediately after the start of treatment and renders the accurate assessment of a true tumor response difficult [1–3]. Emerging evidence of survival prolongation in patients who responded to bevacizumab [4] suggests that it exerts antitumor effects. Reliable means to assess the treatment response and the progression of these tumors addressed with anti-angiogenic agents must be developed.

The response assessment based on neuro-oncology working group (RANO) criteria takes into account increases in the enhanced tumor size, the T2/FLAIR high size, the dose of corticosteroids, and clinical symptoms. Using RANO criteria, it may be possible to identify tumor progression after treatment with bevacizumab because post-treatment the non-enhanced tumor area tends to increase without an increase in the size of the enhanced tumor. This may

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also be reflected by an increase in the size of the T2/FLAIR high-intense lesion. On the other hand, as treatment with bevacizumab may reduce the size of brain edema, it may be difficult to distinguish between true- and pseudo-response at an early point after treatment with bevacizumab.

As the apparent diffusion coefficient (ADC) calculated from diffusion-weighted (DW) images is associated with tumor cellularity [5], it is considered an important biomarker of cancer [6,7]. The ADC has also been used to assess the response of brain tumors to therapy [7] and to predict survival in patients with newly diagnosed glioblastoma [8]. DWI studies at higher diffusion gradient strength (*b*-values) have been used for the diagnosis of acute stroke [9], the assessment of lesion-to-normal contrast in neurodegenerative diseases [10], the prediction of the glioma grade [11], and for the differentiation between glioblastoma and malignant lymphoma [12]. The aim of this study was to evaluate whether RANO criteria and DW imaging including high *b*-value DW (HBDW) imaging could assess the pseudo-response after treatment with bevacizumab. Here we show that HBDW imaging may represent a useful tool for the diagnosis of pseudo-responses in glioblastoma patients treated with bevacizumab.

2. Materials and methods

2.1. Patients and MR imaging

Between September 2008 and May 2011, 10 patients (5 males, 5 females; age range 6–65 years) with recurrent glioma were treated with bevacizumab in our institutions. Recurrence before the administration of bevacizumab was defined by MacDonald criteria [13].

All MRI studies were performed on a 3 T superconducting system (Signa Excite HD 3.0T; GE Medical Systems, Milwaukee, WI, USA). All patients underwent pre- and post-treatment magnetic resonance (MR) imaging including T2- (TR 4800 ms, TE 100 ms, echo train length 18, field-of-view (FOV) 22 cm × 22 cm, matrix size 512 × 320/2NEX, section thickness 6 mm, intersection gap 1.0 mm, 1 acquisition) or FLAIR imaging (TR 10,000 ms, TE 140.0 ms, inversion recovery time 2400.0 ms, FOV 22 cm × 22 cm, matrix size 288 × 160/1NEX, section thickness 6 mm, intersection gap 1.0 mm, 2 acquisitions), gadolinium-enhanced T1-weighted imaging (TR 450 ms, TE 18 ms, FOV 22 cm × 22 cm, matrix size 256 × 192/1NEX, section thickness 6 mm, intersection gap 1.0 mm, 2 acquisitions), and DW imaging at $b = 1000$ and $b = 4000$ s/mm. The parameters at *b*-1000 and *b*-4000 DWI were: 8-channel phased array head coil, TR 5000 ms, TE 66.2 ms (*b*-1000) and TR 5000 ms and TE 96.4 ms (*b*-4000), NEX 1, FOV 220, slice thickness 6 mm, gap 1.0 mm, number of slices 20, data acquisition matrix 128 × 128, scan time 20 s (*b*-1000) and 40 s (*b*-4000).

2.2. Response after treatment with bevacizumab

The response rate was determined using 3 different methods. Under MacDonald criteria [13], the enhanced tumor size was calculated and defined as complete response (CR = disappearance of all enhanced target lesions), partial response (PR = a 50% decrease from the baseline), stable disease (SD = neither PR- nor progressive disease (PD) criteria are met), PD (a 25% increase over the smallest sum recorded or the appearance of new lesions), the clinical assessment and corticosteroid dose were also recorded. Under the criteria of the response assessment in neuro-oncology (RANO) working group [2], factors such as enhanced tumor size, T2/FLAIR high size, dose of corticosteroids, and clinical symptoms were taken into account. At visual inspection, HBDW (*b*-4000) imaging was superior to regular *b*-value based (*b*-1000) DW imaging for the assessment of size changes of high-intense lesions. Therefore, under the third method we calculated the size of the high-intense lesion on HBDW images using its two dimensional measurements and established HBDW criteria where CR = disappearance of all high intensity lesions on HBDW images, PR = a 50% decrease from the baseline of high intensity lesions observed on HBDW images, SD = neither PR nor PD criteria are met, PD = a 25% increase over the smallest sum recorded or the appearance of new DW high lesions on HBDW images.

2.3. Statistical analysis

Statistical analyses were with PRISM version 5.0 (GraphPad Software Inc., La Jolla, CA, USA). The survival time of patients with recurrent glioma was measured from the time of initial treatment with bevacizumab to the time of death or last follow-up. To evaluate prognostic values we performed Kaplan–Meier survival analysis (log-rank test) that incorporated the response to bevacizumab based on MacDonald-, RANO-, or HBDW criteria.

3. Results

Table 1 presents a summary of our patients. Their age ranged from 6 to 65 years (mean 42.5 years, median 40 years). Based on MacDonald criteria, the initial response rate was CR, $n = 4$; PR, $n = 4$; SD, $n = 1$; PD, $n = 1$; under RANO criteria it was CR, $n = 2$; PR, $n = 3$; SD, $n = 3$; PD, $n = 2$, and under HBDW criteria, the initial response rate was PR, $n = 3$; SD, $n = 3$; PD, $n = 4$ patients.

After bevacizumab administration, the enhanced lesion disappeared in 5 tumors and based on MacDonald criteria CR was recorded. In 3 patients there was a decrease in the size of both the T2/FLAIR- and the HBDW high intense lesion; based on RANO and HBDW criteria, PR was recorded (Fig. 1, case 5). These patients are currently alive without recurrence and their treatment with bevacizumab continues.

In some patients the high intensity lesion on T2/FLAIR- and HBDW images increased (Fig. 2, case 1). They were categorized as PD under RANO or HBDW criteria. After continued treatment with bevacizumab, they were recorded as PD. In some patients there was a decrease in the size of the T2/FLAIR high intense lesion after one cycle of bevacizumab. However, in 2 patients the high intense lesion became larger on HBDW images (Fig. 3, case 2) and based on RANO criteria PD was recorded after the continuation of bevacizumab treatment.

We performed Kaplan–Meier survival analysis based on the response rate determined by MacDonald-, RANO-, and HBDW criteria. Under MacDonald criteria we observed no statistical difference between CR/PR- and SD/PD patients (Fig. 4A). Under RANO criteria there was a statistical difference between CR/PR- and SD/PD patients ($p = 0.0153$, Fig. 4B) and under HBDW criteria the difference was more obvious and CR/PR patients survived longer ($p = 0.0152$, Fig. 4C).

4. Discussion

Our study documents that in patients with recurrent glioblastoma, DWI is the superior imaging technique for the diagnosis of pseudo-responses and that HBDW imaging is particularly advantageous. We also show that RANO- is superior to MacDonald criteria because the size of non-enhanced tumors increases after bevacizumab treatment. On the other hand, as the strong effect of bevacizumab against brain edema may produce a decrease in the T2/FLAIR high intense area, this may hide the extension of the tumor area shown as an increase in the T2/FLAIR high intense area. HBDW imaging clearly demonstrated the extent of the tumor area at an early time point after the start of treatment with bevacizumab.