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Case Report

Multiparametric MRI assessment of response to convection-enhanced intratumoral delivery of MDNA55, an interleukin-4 receptor targeted immunotherapy, for recurrent glioblastoma

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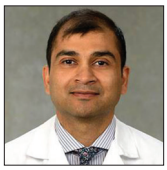

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ABSTRACT

Background: Glioblastoma (GBM) is the most common malignant brain tumor and carries a dismal prognosis. Attempts to develop biologically targeted therapies are challenging as the blood–brain barrier can limit drugs from reaching their target when administered through conventional (intravenous or oral) routes. Furthermore, systemic toxicity of drugs often limits their therapeutic potential. To circumvent these problems, convection-enhanced delivery (CED) provides direct, targeted, intralesional therapy with a secondary objective to alter the tumor microenvironment from an immunologically "cold" (nonresponsive) to an "inflamed" (immunoresponsive) tumor.

Case Description: We report a patient with right occipital recurrent GBM harboring poor prognostic genotypes who was treated with MRI-guided CED of a fusion protein MDNA55 (a targeted toxin directed toward the interleukin-4 receptor). The patient underwent serial anatomical, diffusion, and perfusion MRI scans before initiation of targeted therapy and at 1, 3-month posttherapy. Increased mean diffusivity along with decreased fractional anisotropy and maximum relative cerebral blood volume was noted at follow-up periods relative to baseline.

Conclusion: Our findings suggest that diffusion and perfusion MRI techniques may be useful in evaluating early response to CED of MDNA55 in recurrent GBM patients.

Keywords: Diffusion tensor imaging dynamic susceptibility contrast, Multiparametric MRI, Recurrent glioblastoma, Response assessment

INTRODUCTION

Glioblastoma (GBM) is the most common aggressive primary malignant brain tumor in adults with a miserable prognosis.[16] Targeted toxins consisting of tumor-selective ligands represent a new class of anticancer agents with enhanced specificity.[14,23-25,34] It is reported that 76% of GBMs

overexpress high-affinity receptors (R) for interleukin-4 (IL-4), a pleiotropic immunoregulatory cytokine that regulates immune responses and tumor microenvironment with poor clinical outcomes in GBM.[8] Moreover, overexpression of IL-4 and IL-13 receptors on neoplastic cells provides specific targets for therapeutic agents for cancer therapy.[9]

At present,[27] MDNA55, an IL-4R-directed toxin, is being studied in a Phase 2b trial in recurrent GBM patients. It is coinfused with gadolinium-based contrast agent and delivered as a single intratumoral infusion using convection enhanced delivery (CED). It is associated with a good safety profile with no systemic toxicities or drug-related deaths. We report our initial experience in assessing early and objective treatment response to MDNA55 in a patient with recurrent GBM utilizing multiparametric MRI.

CLINICAL DESCRIPTION

A 57-year-old female with the right occipital recurrent GBM (IDH-1 wild-type, MGMT promoter methylated, with EGFR amplification) was treated with MRI-guided convection-enhanced intratumoral delivery of MDNA55. She underwent initial resection 32 months before this presentation followed by standard-of-care chemoradiation therapy. Her follow-up MRI demonstrated increasing size of enhancing lesion along the anteroinferior aspect of the right occipital resection cavity with elevated relative cerebral blood volume (rCBV), consistent with progressive recurrent malignant glial neoplasm. At this time, her presenting symptoms included memory deficits, confusion, persistent fatigue, and worsening gait instability.

Placement of catheters and infusion of MDNA55

CED catheters were precisely placed under stereotactic guidance after importing the neuronavigation sequences to Brainlab Curve-100 workstation. Two entry points were planned for the minimally invasive trajectory using the "Overview" view to develop a 3D model of the target recurrent tumor and surrounding neural and vascular structures. The catheters were secured in a 14 French Foley catheter (red rubber tubing), stab wounds were then closed with 3-0 Nylon (Neurolon) sutures and the patient was transferred, intubated to the MRI suite [Figure 1]. The catheter position was confirmed in ideal location as noted by the release of gadolinium during MRI [Figure 2]. The patient tolerated the procedure well and remained neurologically intact postoperatively. The catheters were closely monitored in the Neuro-Intensive Care Unit and MDNA55 was infused per protocol at 0.5 ml/h.

Imaging response assessment

The patient underwent serial MRI scans including a baseline and 1, 3-month follow-up MRI on a 3T scanner using a 12-channel, phased array head coil. The MRI protocol included anatomical images, diffusion tensor imaging (DTI), and dynamic susceptibility contrast perfusion-weighted imaging (DSC-PWI) using parameters as described previously.[7,31] On conventional imaging, there was a significant reduction of contrast enhancement which was observed during this period, likely indicative of tumor necrosis. Increased mean diffusivity (MD) along with decreased fractional anisotropy (FA) and $rCBV_{max}$ was noted at follow-up relative to baseline consistent with tumor response, with reduced cellularity and vascular normalization [Figures 3 and 4].

Clinical follow-up

She did well immediately after the infusion, was neurologically intact, and discharged to a rehabilitation facility on day 2 after the procedure. She was readmitted after approximately 1½ months with declining Karnofsky performance score (KPS of 50), persistent nausea and vomiting, unsteadiness of gait, and somnolence, and was found to have hydrocephalus for which a ventriculoperitoneal shunt was placed. She eventually experienced tumor progression and was not considered a candidate for additional treatment, and hence, was transferred to hospice for palliative care.

DISCUSSION

We demonstrated imaging findings suggestive of a positive early response to convection-enhanced intratumoral delivery of MDNA55, an IL-4 receptor targeted immunotherapy, in a patient with recurrent GBM. Reduced tumor volume, increased MD, decreased FA, and markedly reduced rCBV were observed from contrast enhancing regions of neoplasm. As tissue immunophenotyping was not performed, it is speculative whether the favorable local response was due to a direct pharmacological effect, or an induced immunomodulatory effect, or a combination of these.

The IL-4R is highly expressed in multiple tumor types including 76% of GBMs, spurring tumor growth.[14] MDNA55 is a targeted fusion protein comprising a genetically engineered circularly permuted IL-4 fused to a truncated and modified version of pseudomonas exotoxin-A (PE). MDNA55 binds to IL-4R on surfaces of tumor cells and entire complex is endocytosed. PE is cleaved off by furin-like proteases found in the endosome and released into the cytosol. Free PE causes ADP-ribosylation, deactivation of elongation factor-2, leading to inhibition of protein synthesis eventually causing tumor cell death. Because normal brain tissue does not express this receptor, IL-4R represents an attractive therapeutic target.[9,14,23,24,34] A brief overview of action mechanism of MDNA55 is presented in [Figure 5].

Conventional MRI is limited in evaluating treatment response in GBM patients, due to lack of specificity,

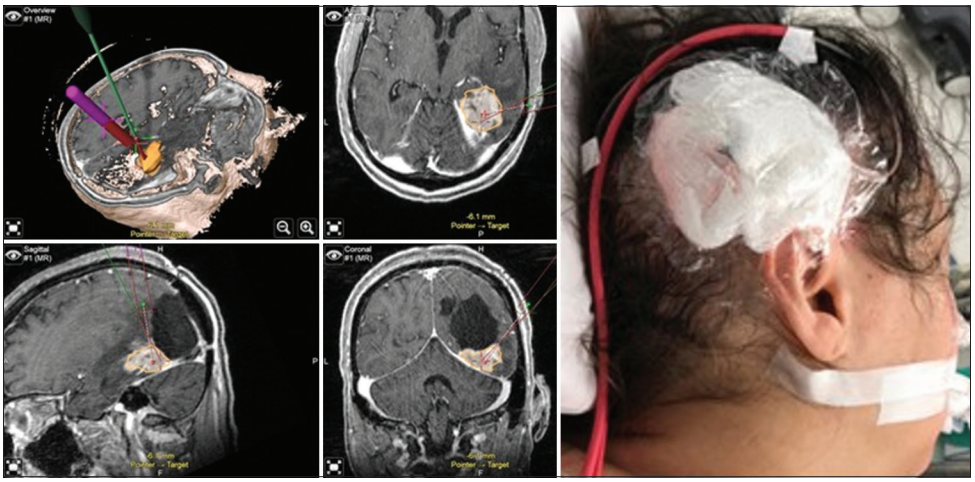

Figure 1: Intraoperative neuronavigation (Brainlab®, Munich, Germany) demonstrating lesion mapping and trajectory planning through topographic, axial, sagittal, and coronal views (clockwise, left panel). Postoperative wound dressing and secured drug delivery catheter, reflecting the right occipital-parietal entry point (right panel).

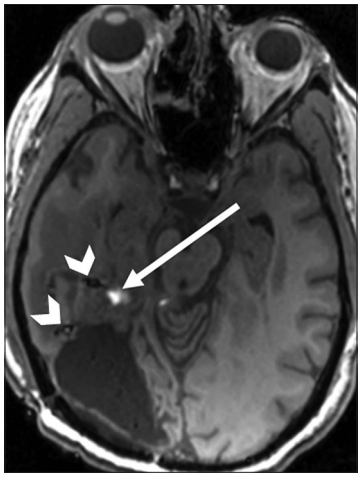

Figure 2: Intraprocedural MRI after placement of two flexible catheters for convection-enhanced delivery of MDNA55. Catheter position (white arrowheads) confirmed in ideal location by the release of gadolinium contrast agent (white arrow).

especially in the setting of immunotherapy.[11] However, advanced MRI techniques such MR spectroscopy, diffusion, and perfusion MRI have been used successfully for determining prognosis, predicting, and assessing treatment response to different therapeutic regimens in these patients.[1,2,6,10,13,19,22,28-30,32,33] On DTI, successful treatment is exhibited by increase in MD, and decrease in FA values reflecting destruction of tumor cells and reduction of barriers to proton motion.[5,20,21,32] From our case, we observed large % decreases (33–37%) in FA at follow-up periods relative to baseline indicating favorable treatment response. These results are in conformity with the previous studies reporting that reduced FA is associated with positive treatment outcomes. The reduction in FA may be due to reduced cell density and/or random arrangement of neoplastic cells following immunotherapy. Even though FA is considered as a valuable predictive parameter,[10] some studies did not find any significant differences in FA values between tumor progression and treatment effects (pseudo-progression).[1] Variable trends in FA values have also been reported at follow-up periods relative to baseline in GBMs treated with immunotherapy.[33] The irregular trends in FA after treatment may also arise because of varying degree of pathological events including reduced cellular density, decreased cellular proliferation, demyelination, and/or astrogliosis occurring within the tumor beds following therapy.[3] Given that FA may not always be reliable in assessing treatment response, our results should be treated with caution and should be validated in larger future studies.

Neovascularization (formation of new blood vessels) is a common feature of GBMs that account for high tumor perfusion as seen on DSC-PWI-derived CBV maps.[17] Several studies have reported reduced rCBV in GBMs following chemoradiation therapy, anti-angiogenic therapy, and immunotherapy suggesting the potential utility of rCBV in evaluating treatment response.[2,29,33] Fibrinoid necrosis, endothelial injury, and occlusion of blood vessels have been proposed as potential reasons for decreased rCBV in treated brain tumors.[18] In agreement with these studies, reduced $rCBV_{max}$ was noted in the present case suggesting reduced vascularity and tissue perfusion within the tumor bed following MDNA55 infusion. IL-4R is known to be part of the angiogenic signaling pathway, secreted by activated T lymphocytes, basophils, and mast cells,[26] which could explain the dramatic decrease in rCBV and reduction in contrast enhancement.

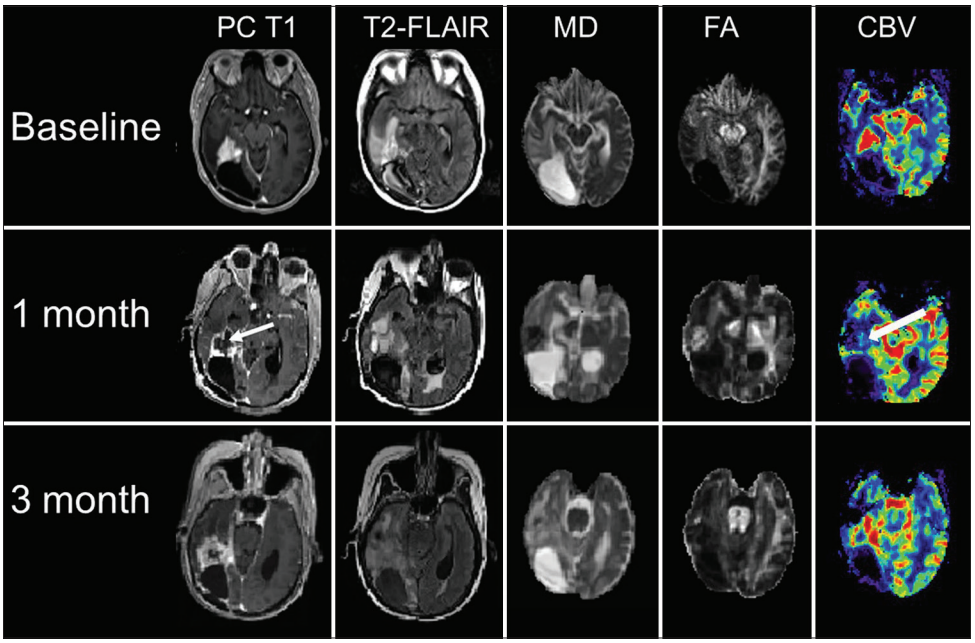

Figure 3: Axial coregistered postcontrast T1-weighted image (PC T1), T2-FLAIR, and corresponding mean diffusivity (MD), fractional anisotropy (FA), and cerebral blood volume (CBV) maps are shown at baseline, 1-month, and at 3-month follow-up periods. There was a striking reduction of contrast enhancement, and CBV (white arrows), more apparent at 1-month follow-up compared to the baseline, with increased MD and decreased FA.

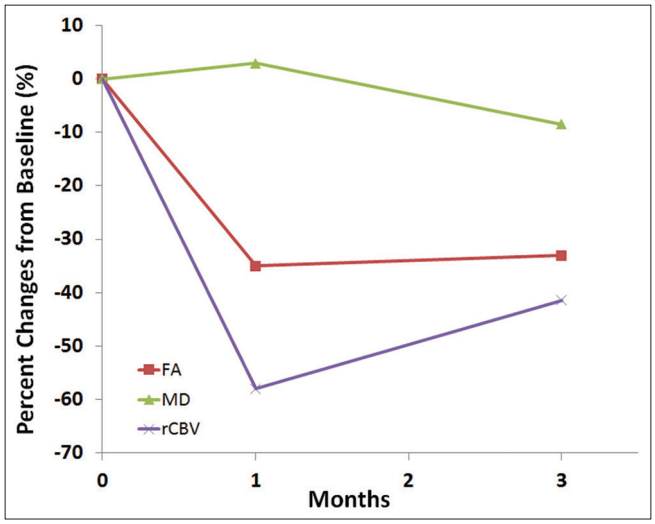

Figure 4: Percent changes in MR parameters (MD, FA, and rCBV) at follow-up periods relative to baseline. MD: Mean diffusivity, FA: Fractional anisotropy, rCBV: Relative cerebral blood volume.

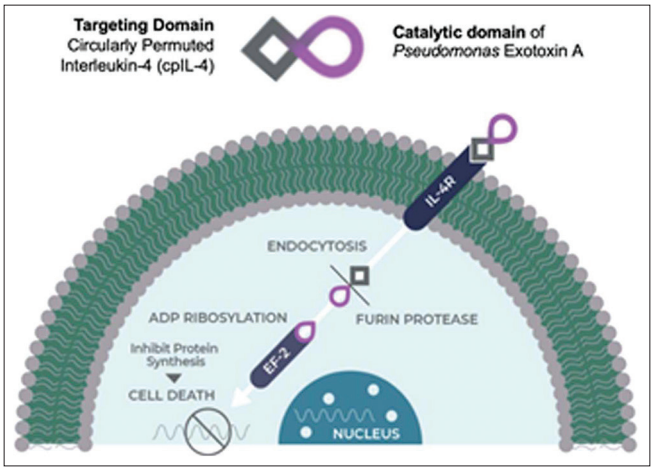

Figure 5: A schematic representation for action mechanism of MDNA55 (Courtesy, Medicenna Biopharma Inc.).

Despite showing promising findings, clinical utility of CBV maps sometimes may be constrained by limitations that include susceptibility artifacts caused by microhemorrhages present within the tumor bed.[12] In recent times, dynamic contrast enhanced (DCE) MRI-derived parameters, such as volume transfer constant (K^{trans}) and volume fraction of plasma space in tissue (v_p) that are known to be less prone to susceptibility artifacts, have also been used in assessing the treatment response in GBMs.[4,5,15] Unfortunately, we did not have the availability of DCE-MRI data at all time points in our case due to time constraints. Nevertheless, we did not find any evidence of microhemorrhages within the tumor beds and we believe that CBV maps were reliable enough in assessing the effects of immunotherapy on tumor vasculature in our case.

We believe that multiparametric analysis combining the unique strengths of DTI and DSC-MRI techniques, as performed in the present case, could contribute to a more

comprehensive assessment of treatment response in these patients.

CONCLUSION

Advanced MRI techniques could be a useful adjunct in assessing early response to CED of MDNA55 in recurrent GBM patients. However, this promising finding warrants further validation in future, larger clinical trials.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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