IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Contralateral transient contrast enhancement in a patient with IDH1wt MGMT promoter-methylated GBM responding to TMZ and individualized multimodal immunotherapy

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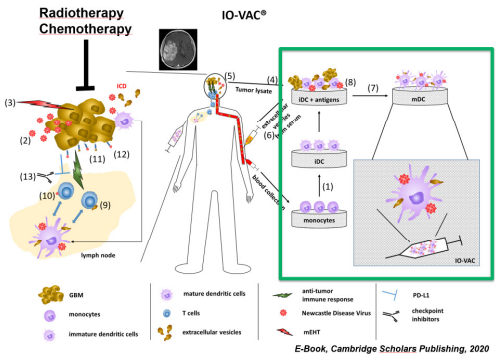
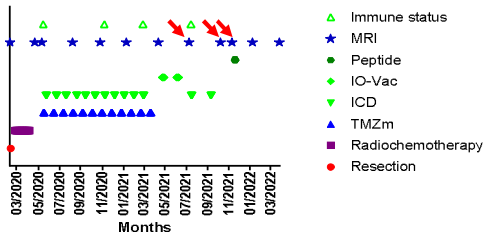
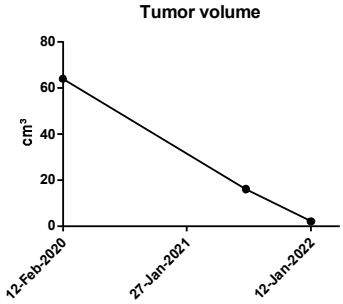
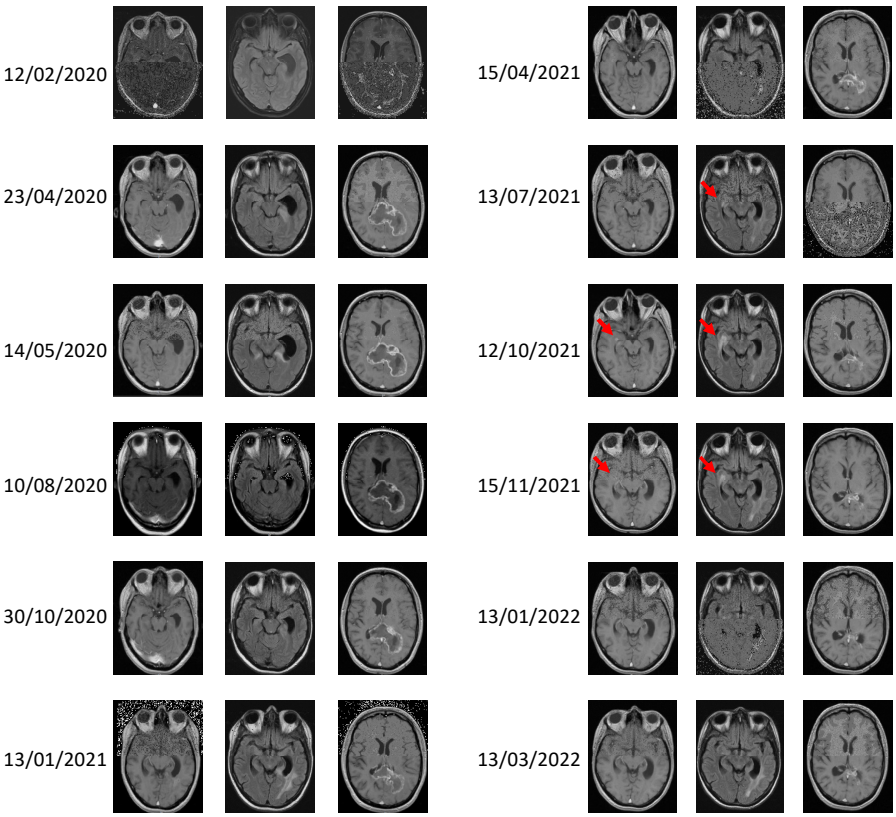
Introduction. Immunotherapy-induced MRI changes remain challenging when treating GBM patients with immunotherapy as part of a combined treatment. The iRANO criteria provide a decision-tree in order to avoid over- and under-treatment reactions when contrast-enhancing lesions become visible and should be interpreted. We report a patient with inoperable IDH1wt MGMT promoter-methylated GBM treated with TMZ and individualized multimodal immunotherapy. We observed the appearance of a contralateral lesion with contrast-enhancement, interpreted by several colleagues as relapse, but disappearing again without initiation of any oncologic treatment.

The principle of Individualized Multimodal Immunotherapy. During a vaccination cycle, immature dendritic cells (DCs) are differentiated *ex vivo* out of adherent peripheral blood monocytes in the presence of 800 U/ml IL-4 and 1000 U/ml GM-CSF. DCs are loaded on day 5 with autologous tumor antigens, obtained via tumor lysate or obtained from serum containing tumor-derived antigenic extracellular microvesicles and apoptotic bodies, induced via 5 daily **immunogenic cell death immunotherapies**. DC maturation is induced with NDV (10^5 infectious particles per 10^6 DCs) and a cytokine cocktail (1000 U/ml IL-6, 1100 U/ml TNF-a and 1900 U/ml IL-1b). **Active specific immunotherapy**: an intradermal injection of autologous loaded mature DCs is administrated on day 8, combined with an extra ICD immunotherapy. Two full vaccination cycles are administered with three weeks interval. **Modulatory immunotherapy** is defined for each patient. ***IO-VAC® is an approved medicinal product by the German authorities (DE_NW_04_MIA_2015_0033, DE_NW_04_MIA_2020_0017).***









Case. We report a 34-year female, 34 weeks pregnant, who presented with epilepsy, and was diagnosed with inoperable IDH1wt MGMT promoter-methylated GBM after biopsy. On MRI, the left occipital lesion was mostly cystic-necrotic with peripheral contrast enhancement, and crossed over the corpus callosum to the right. The volume was calculated as 64 cm^3 (abc/2 formula). She was treated with radiochemotherapy and 12 TMZm cycles. Within each TMZ cycle, 5 days of immunogenic cell death (ICD) immunotherapy (5 injections with Newcastle Disease Virus and 5 sessions of modulated electro-hyperthermia (Oncotherm 50 min 40-60 Watt)) were added from days 8 to 12. After all chemo-/ICD-therapy we continued with active specific immunotherapy: two autologous mature monocyte-derived dendritic cell vaccines loaded with ICD therapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies (**IO-Vac®**). One month after the second **IO-Vac®**, 17 months after diagnosis, a transient right FLAIR-visible region showed expansion (↘), and three months later also diffuse contrast enhancement, which was confirmed in a control scan one month later. The original tumor was meanwhile reduced to 16 cm^3. However, in further scans, two and four months later, the contrast enhancement was disappeared, and the pathologic area on FLAIR was diminished. The original tumor size was reduced to 2 cm^3, two year after first diagnosis. She showed allergic skin reactions to TMZ, which was covered with systemic histamine intake. There were no side effects related to multimodal immunotherapy.

Conclusion. Transient MRI changes can be observed even in distance from the original tumor and can be interpreted as immune-mediated effects, rather than relapse, when the original tumor is responding.