IOZK | NEW PERSPECTIVES IN CANCER THERAPY

Integration of individualized multimodal immunotherapy for adults with IDH1 wild-type GBM

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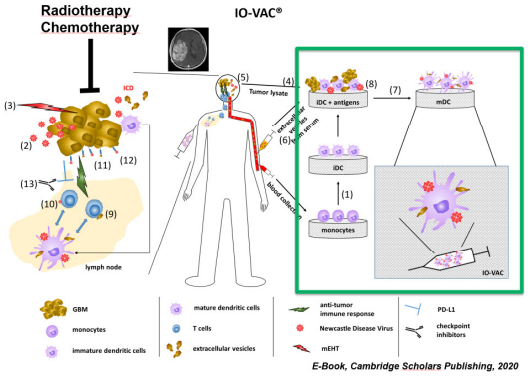
Introduction. A synergistic activity between maintenance temozolomide (TMZm) and individualized multimodal immunotherapy (IMI) during/after first-line treatment has been suggested for improving the overall survival (OS) of adults with IDH1 wild-type MGMT promoter-unmethylated (unmeth) GBM (Genes&Immunity 2022). We aimed to expand the data and include the OS of MGMT promoter-methylated (meth) adults with GBM.

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).***

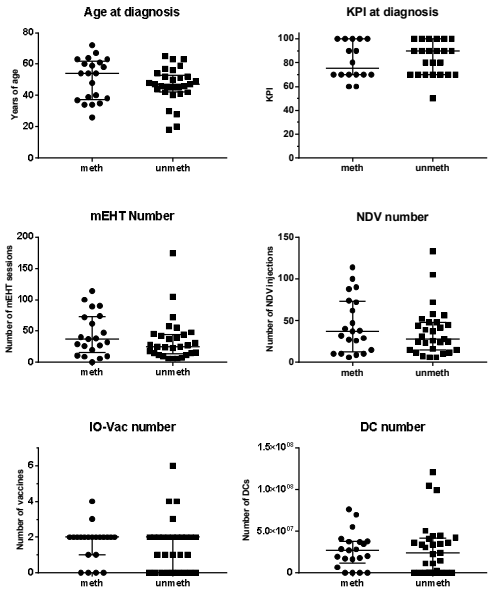


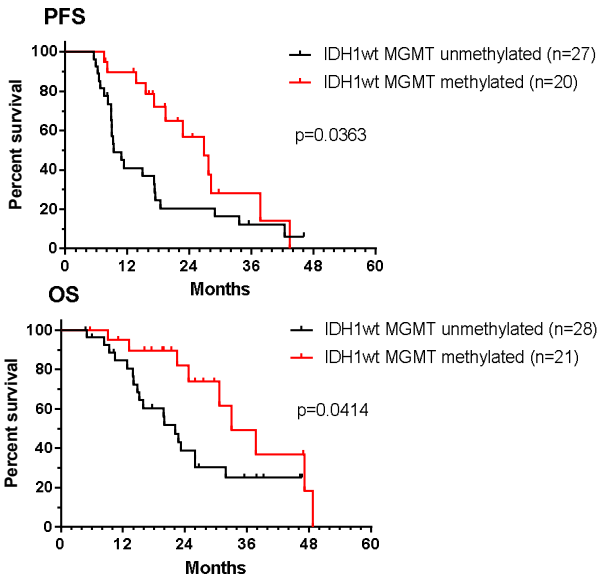
E-Book, Cambridge Scholars Publishing, 2020

Patients. Unmeth (10 f, 18 m) and meth (11 f, 10 m) patients treated between 27/05/2015 and 01/01/2022 were retrospectively analysed. There were no differences in age (median 48y, range 18-72y) or Karnofsky performance index (median 70, range 50-100). The extent of resection was not significantly different between both patient groups (<R0 ,R0, not documented: 13/5/3 in unmeth and 11/7/10 in meth patients)

Treatment. Patients were treated with neurosurgery, radiochemotherapy and Temozolomide maintenance chemotherapy (TMZm). Within each TMZm cycle, 5 days of **immunogenic cell death (ICD) immunotherapy** (5 injections with Newcastle Disease Virus (NDV) and 5 sessions of modulated electro-hyperthermia (mEHT, 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®**), combined with individualized **modulatory immunotherapy**. Finally, treatment was continued with maintenance ICD immunotherapy and modulatory immunotherapy.

Results. Results in unmeth and meth patients were compared. Basic blood samplings were usually performed after the radiochemotherapy. There were no differences in blood counts, lymphocyte subpopulations, proportion of patients with circulating tumor cells (without or with PDL1 mRNA expression), oxidative stress or total anti-oxidative capacity. There were no differences in number of vaccines (median 2; range 0-6), total number of DCs (median 25.6x10e6; range 0-120.58x10e6), number of NDV injections (median 31; range 6-133) and number of mEHT sessions (median 28; range 0-174). However, PFS and OS were significantly different for unmeth *versus* meth patients. Median PFS was 9m *versus* 27m (log-rank test: p=0.036) with 2-y PFS of 20.4% (CI95%: +17.3, -12.9+) resp. 56.6% (CI95%: +20.4, -27.7). Median OS was 22m *versus* 33m (log-rank test: p=0.041) with 2-y OS of 38.8% (CI95%: +18.5, -18.8+) resp. 82.2% (CI95%: +11.8, -28.7). There were no side effects related to multimodal immunotherapy.





Conclusion. The OS in both MGMT promoter-unmethylated and -methylated adults with IDH1 wildtype GBM strongly exceeded reported (Lancet Oncol 2009) data with radiochemotherapy and TMZm alone (median OS 12.6 resp. 23.4m; 2y-OS 14.8% resp. 48.9%). The MGMT promoter methylation status remains a strong prognostic factor when IDH1wt GBM patients are treated with radio/chemo/immunotherapy. The addition of IMI during/after standard of care should be prospectively explored using an external control arm.