Modulated electrohyperthermia as part of immunogenic cell death treatment in pediatric neuro-oncology

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Modulated electrohyperthermia as part of immunogenic cell death treatment in pediatric neuro-oncology

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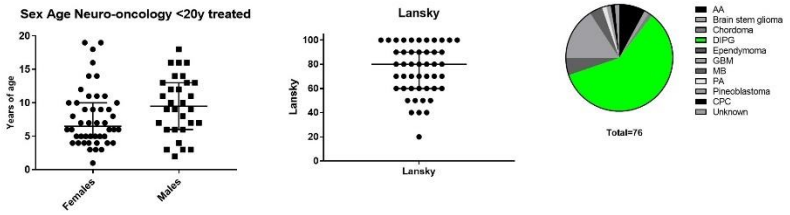
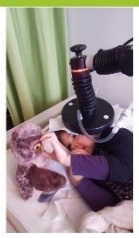
Introduction. The induction of immunogenic cell death (ICD) becomes an important treatment methodology in cancer. Convincing data demonstrate that modulated electrohyperthermia (mEHT) contribute to ICD. No data have been reported about the use of mEHT in a large pediatric brain cancer population.

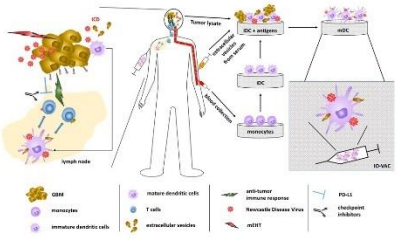
Patients. We retrospectively analyzed a series of 76 children treated at IOZK with multimodal immunotherapy consisting of the combination of Newcastle Disease Virus (NDV) injections with mEHT and autologous dendritic cell vaccines ***IO-VAC®***.

Patient characteristics





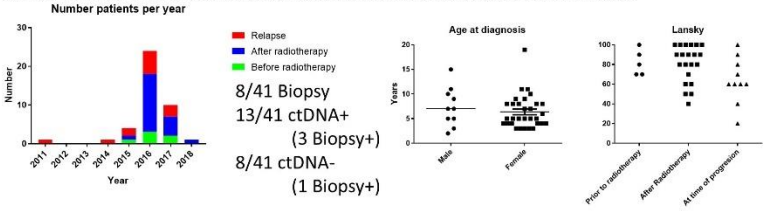
The principle of *IO-VAC®*. Full vaccination cycles are administered with three weeks interval. Each full vaccination cycle consists of NDV and mEHT administrations at days 1 to 5 and at day 8. An intradermal injection of autologous mature dendritic cells (DCs) loaded with autologous tumor antigens is administrated at day 8. Immature 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 at day 5 with autologous tumor antigens, obtained via tumor lysate or obtained from serum after induction of tumor-derived antigenic extracellular microvesicles, induced via ICD by mEHT and NDV. DC maturation is induced with NDV (10^5 infectious particles per 10^6 DCs) and the cytokine cocktail 1000 U/ml IL-6, 1100 U/ml TNF-a and 1900 U/ml IL-1b. GMP-approved culture medium and cytokines are purchased from Cellgenix (Freiburg, Germany). ***IO-VAC® is an approved medicinal product by the German authorities (DE-NW-04-MIA-2015-0033).***

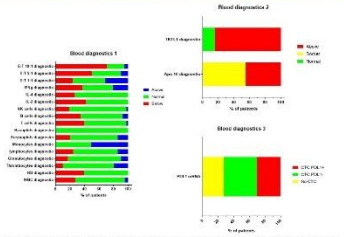


Results. There were 46 females and 30 males with a median age of 6.5 resp. 9.5 years (range 1-19y resp. 2-18y). Diagnoses were anaplastic astrocytoma (6), Brain stem glioma (1), chordoma (1), DIPG (45), Ependymoma (4), GBM (12), medulloblastoma (3), pilocytic astrocytoma (1), pineoblastoma (1), choroid plexus carcinoma (1), unspecified (1). In total 811 mEHT sessions were given. Median number of mEHT sessions per child were 15, ranging up to 53. In all cases, mEHT doses were 40 Watt during 40 minutes. Treatments were feasible without sedation. There were no intervention-related side effects. NDV injections were associated to the mEHT sessions. Multimodal immunotherapy included the DC vaccinations with ***IO-VAC®***. In total 77 ***IO-VAC®*** vaccines were produced, and in median 2 (range 0-4) ***IO-VAC®*** vaccines were given per child. The use of PanTum Detect tests (TKTL1 and Apo10) seemed reliable to monitor on daily basis the response to ICD treatment and over the treatment course. Median overall survival of 28 DIPG children treated with multimodal immunotherapy as part of their first line treatment showed a median overall survival of 14 months. Remarkable long-term remissions were also observed in a child with relapsed pineoblastoma and a child with metastasized Myc-amplified medulloblastoma group 3.

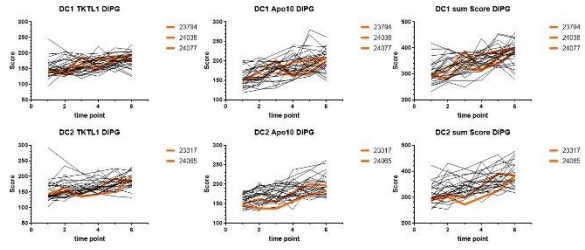
Data on 41 children with DIPG treated with multimodal immunotherapy

The patient group is splitted into a subgroup treated with immunotherapy prior to radiotherapy, a second subgroup treated with immunotherapy after radiotherapy, and a third subgroup treated with immunotherapy at the time of progressive disease. Depicted are number of patients treated per year; Age and sex distribution, and Lansky score.

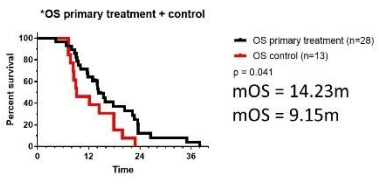




Blood values at time of start of immunotherapy. Left: immune parameters. Right top: TKTL1 and Apo10 score. Right bottom: mRNA expression for PDL1 on circulating tumor cells when detected.



Intracellular expression of TKTL1 (left), Apo10 (middle) and sum of both (right) in CD144+CD16- gated peripheral blood white blood cells, measured during first (DC1) or second (DC2) vaccination cycle. Measurements are performed at day 1/2/3/4/5/8 of each cycle. From day 1 to day 5, NDV injections and mEHT treatments are given. Each line represents the data of a neuro oncologic patient, most adults with GBM. The colored lines represent available data from DIPG children treated with DC vaccination cycles.



Overall survival of children treated with multimodal immunotherapy in the context of first line treatment (black) , or at time of first progression after first line treatment (red). The latter serves as control to the former taking into account the selection biases of patients coming to IOZK for treatment. OS is always calculated from the time of first diagnosis. The figure suggests that multimodal immunotherapy as part of first line treatment gives better overall survival outcome as compared to patients with similar disease and family profile who were treated at time of progressive disease.

Conclusion. Modulated electrohyperthermia (mEHT) for children with brain cancer as part of multimodal immunotherapy is feasible and safe. Response to treatment could be monitored. Dosing of mEHT is now expanded to 60 Watt. First experiences demonstrate clinical feasibility. Multimodal immunotherapy contributed to improved tumor control and overall survival.