Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors

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Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors

Stefaan W. Van Gool, Jennifer Makalowski, Wilfried Stuecker
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Abstract
Immunotherapy has become a fourth pillar of anticancer treatment. Modern immunotherapy consists of multiple strategies all aimed to induce an antitumoral immune response including immunologic memory. Antibody therapy is considered as passive immunotherapy. Immunogenic cell death induction with oncolytic viruses like Newcastle disease virus (NDV), and techniques like local modulated electrohyperthermia (mEHT) aim to induce immunogenic cell death (ICD) of tumor cells thereby creating the necessary danger signals in tumors and a subsequent active immunization. Autologous mature dendritic cells (DC) loaded with tumor antigens are considered as active specific immunotherapy aimed directly to stimulate tumor-reacting T cells. Actual tumor antigens can be derived from NDV/mEHT-induced serum-derived antigenic extracellular microvesicles. Total body hyperthermia in order to stimulate the innate immune system, ATRA in order to deplete myeloid derived suppressor cells, low dose cyclophosphamide to deplete regulatory T cells, checkpoint blockers to release the immune system all are considered as immunomodulatory strategies. In the presentation, data will be discussed on a group of patients with glioblastoma multiforme and a group of children with diffuse intrinsic pontine glioma, for whom multimodal immunotherapy was part of the multi-treatment strategy including radiochemotherapy and chemotherapy. The data suggest that mEHT can contribute as direct anti-tumor treatment, as immune stimulator via ICD and as tool for yielding actual tumor antigens.
Modulated electrohyperthermia (mEHT) as part of multimodal immunotherapy for brain tumors

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First results on survival from a large Phase 3 clinical trial of an autologous dendritic cell vaccine in newly diagnosed glioblastoma

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Amd Slegers

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Prof. Dr. Volker Schirmacher
MD-PhD Stefaan Van Gool
Dr. Wilfried Stücker
Dr. Matthias Domogalla

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Prüfungsschema praktische Abgrenzung zwischen individuellem Heilversuch und klinischem Experiment

Eingriff oder Behandlungsweise

ja

Eingriff oder Behandlungsweise

nein

anerkannter medizinischer Standard

ja

Gewinnung von aussagekräftigen und verifizierbaren Daten und Ergebnissen

nein

Standardbehandlung

individueller Heilversuch oder klinisches Experiment

individueller Heilversuch

klinisches Experiment

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Diagnostic categories total group < September 2018

Albis Cumulative number category

Breast Cancer
Digestive Oncology
Endocrine Oncology
Gynecological Oncology
Head&Neck Cancer
Hemato-Oncology
Medical Oncology
ND
Neuro-Oncology
Orthopedic Oncology
Pneumology
Urology oncology

Number = 2073
Molecular mechanisms of cell death: recommendations of the Nomenclature Committee on Cell Death 2018

Lorenzo Galluzzi1,2,3, Illo Vitale4,5 et al.
Research Paper

Modulated electro-hyperthermia induced loco-regional and systemic tumor destruction in colorectal cancer allografts

Tamas Vancsik1, Csaba Kovago2, Eva Kiss1, Edina Papp3, Gertrud Forika1, Zoltan Benyo4, Nora Meggyeshazi5, Tibor Krenacs6,7

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Newcastle disease virotherapy induces long-term survival and tumor-specific immune memory in orthotopic glioma through the induction of immunogenic cell death

Carollen A. Koks1, Abhishek D. Garg2, Michael Ehrhardt3, Matteo Riva1, Lien Vandenberk1, Louis Boon4, Steven De Vleeschouwer5,6, Patrizia Agostinis2, Norbert Graf7 and Stefaan W. Van Gool1,4,7

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6. Department of Neurosurgery, University Hospitals Leuven, Herestraat 49, Leuven, Belgium
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Isolation, differential splicing and protein expression of a DNase on the human X chromosome.

Coy, J.E.¹, Velthagen, I., Himmele, R., Delius, H., Poustka, A. and Zentgraf, H.

Abstract
A systematic search for genes differentially expressed in human tissues resulted in the isolation of a gene encoding a protein with high homology to DNase I. In addition to the recently described cDNA sequence (Parrish et al., 1995) we have isolated a transcript, alternatively spliced in the 5' non-coding region. The gene is located between the QM and the XAP-2 gene in Xq28 and encodes a 302 amino acid protein with 39% identity to human DNase I. Besides a high homology at the nucleotide and amino acid level, most exon-intron boundaries of DNase I and DNase X are identical, indicating that both genes may have evolved from a common ancestor. The predicted function was verified by expression of a recombinant protein in an inducible bacterial system and detection of DNase activity. In contrast to DNase I a 18 kdal amino terminal fragment of the full length 35 kdal protein exhibited DNase activity.
Database 20180101

Database. 2347 records
GBM label. 282 records
GBM label + Albis number. 198 records
GBM label + Albis number + treatment. 122 records

Now we classified in the classification system the entities 1 to 3:
- Classification 1: 109 primary GBM, 1 patient loss of follow up for OS.
- Classification 2: 12 secondary GBM (IDHmut or LGG mentioned)
- Classification 3: 1 GBM DMG

We classified further towards event number

<table>
<thead>
<tr>
<th>Event</th>
<th>Primary (or unknown) GBM</th>
<th>Secondary GBM</th>
<th>GBM DMG</th>
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</thead>
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<td>56</td>
<td>2</td>
<td>1</td>
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<tr>
<td>Event 2</td>
<td>31</td>
<td>1</td>
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<td>Event 3</td>
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<td>Event 4</td>
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<td>Event 5</td>
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<td>3</td>
<td></td>
</tr>
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<td>Event 6</td>
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<tr>
<td>Event 7</td>
<td></td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

Retrospective summary of patients treated as "Individueller Heilversuch"
Standard therapy supplemented with immunogenic cell death therapy during and subsequent multimodal immunotherapy for GBM

Table 1: Patient characteristics

<table>
<thead>
<tr>
<th>Number</th>
<th>Sex</th>
<th>Age</th>
<th>Karnofsky</th>
<th>Location</th>
<th>Methylation</th>
<th>Extent of resection</th>
<th>TMZm²</th>
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<tbody>
<tr>
<td>22731</td>
<td>M</td>
<td>54</td>
<td>100</td>
<td>Temporal left</td>
<td>Methylated</td>
<td>R1</td>
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<tr>
<td>22752</td>
<td>F</td>
<td>61</td>
<td>70</td>
<td>Temporoparietal right</td>
<td>Methylated</td>
<td>R0</td>
<td>0</td>
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<tr>
<td>22866</td>
<td>F</td>
<td>44</td>
<td>70</td>
<td>Occipital right</td>
<td>Methylated</td>
<td>R0</td>
<td>0</td>
</tr>
<tr>
<td>22878</td>
<td>M</td>
<td>67</td>
<td>70</td>
<td>Occipital links</td>
<td>Not methylated</td>
<td>R0</td>
<td>0</td>
</tr>
<tr>
<td>23103</td>
<td>M</td>
<td>42</td>
<td>100</td>
<td>Parietal right</td>
<td>Not methylated</td>
<td>S nd²</td>
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<tr>
<td>23260</td>
<td>F</td>
<td>62</td>
<td>70</td>
<td>Parietal left</td>
<td>Methylated</td>
<td>R0</td>
<td>0</td>
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<tr>
<td>23346</td>
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<td>37</td>
<td>70</td>
<td>Frontal right</td>
<td>Methylated</td>
<td>R1</td>
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</tr>
<tr>
<td>23565</td>
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<td>Occipital right</td>
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<td>80</td>
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<td>61</td>
<td>100</td>
<td>Frontal right</td>
<td>Not available</td>
<td>S nd</td>
<td>3</td>
</tr>
<tr>
<td>23696</td>
<td>M</td>
<td>65</td>
<td>90</td>
<td>Temporal left</td>
<td>Not methylated</td>
<td>S nd</td>
<td>0</td>
</tr>
<tr>
<td>23769</td>
<td>M</td>
<td>67</td>
<td>100</td>
<td>Frontal right</td>
<td>Not available</td>
<td>R0</td>
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<tr>
<td>23806</td>
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<td>60</td>
<td>100</td>
<td>Temporal right</td>
<td>Methylated</td>
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<tr>
<td>23834</td>
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<td>60</td>
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<td>Frontal left</td>
<td>Not available</td>
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</tr>
<tr>
<td>23877</td>
<td>M</td>
<td>44</td>
<td>100</td>
<td>Parietal left</td>
<td>Not methylated</td>
<td>R0</td>
<td>0</td>
</tr>
</tbody>
</table>

1 S nd: extent of resection not documented.
2 Number of maintenance TMZ courses prior to combining TMZ + NDV/mEHT.

Yau Gool SW, et al. AOCR 2018
Retrospective summary of patients treated as „Individueller Heilversuch“
Evolution PDL1 mRNA expression in CTC

Evolution of Apo10+TKTL1

Evolution of IL-4/IFN-g

PFS 5d3d

Vau Gool SW, et al. AOCR 2018

Retrospective summary of patients treated as „Individueller Heilversuch“
OS 5d3d

Percent survival

Months

DIPG children

Consulted (n=101, 71%)
Treated (n=41, 29%)

Retrospective summary of patients treated as „Individueller Heilversuch“

Retrospective summary of Children treated as „Individueller Heilversuch“
Retrospective summary of Children treated as „Individueller Heilversuch“
Phase I read-out: feasibility, no major toxicity
   * NDV infusions
   * modulated Electrohyperthermia
   * DC vaccination

Phase IIa read-out: response to treatment

Retrospective summary of Children treated as "Individueller Heilversuch"
IL-4/IFNγ evolution

PDL1 mRNA Evolution

Retrospective summary of Children treated as „Individueller Heilversuch“

Retrospective summary of Children treated as „Individueller Heilversuch“
Tumor surveillance using liquid biopsy in diffuse intrinsic pontine glioma

Introduction

Immuno-therapeutic approaches are being developed to treat diffuse intrinsic pontine glioma (DIPG), the most common childhood brain tumor. NGS is the gold standard for identifying mutations in DIPG, and is limited by the amount of tumor tissue available for sequencing. In this study, we used liquid biopsy to detect, characterize, and monitor DIPG-specific mutations over time. We used a targeted NGS panel to identify somatic mutations in DIPG patients. The panel was designed to include the most commonly mutated genes in DIPG, and to detect both known and novel mutations. The panel was optimized for sensitivity and specificity, and was able to detect mutations with a sensitivity of 10^{-5}.

Methods

DIPG patients were enrolled and their tumor tissue was collected in sterile tubes. DNA was extracted from tumor tissue and plasma using standard protocols. The DNA was then used to perform targeted NGS sequencing of the panel. Results were interpreted using software that identifies potential targets for further investigation.

Results

- **Patient 1:** Mutation in the IDH1 gene was detected in the plasma. This mutation was not detected in the tumor tissue.
- **Patient 2:** Mutation in the TERT gene was detected in the plasma. This mutation was not detected in the tumor tissue.
- **Patient 3:** Mutation in the EGFR gene was detected in both the tumor tissue and the plasma.

Conclusions

- Liquid biopsy is a promising tool for monitoring DIPG patients over time.
- Early detection of mutations in plasma may provide valuable information for treatment decision-making.

Future directions

- Further validation of the panel in a larger cohort of patients is needed.
- Development of targeted therapies based on liquid biopsy findings is currently being explored.

Acknowledgments

This study was supported by the Children's National Health System and the National Institute of Neurological Disorders and Stroke (R01 NS093325).

**PFS primary treatment + control**

- **PFS primary treatment (n=22)**
- **PFS Control (n=13)**

\[ p = 0.0084 \]
Oncothermia Journal, Volume 24, October 2018

Retrospective summary of Children treated as "Individueller Heilversuch"

*OS primary treatment + control

- OS primary treatment (n=28)
- OS control (n=13)

\[ p = 0.0289 \]

Retrospective summary of Children treated as "Individueller Heilversuch"

OS primary treatment → RT

- IT after RT (n=22)
- IT before RT (n=6)
Multimodal immunotherapy as part of Multimodal treatment for patients with cancer

Ideal scenario = early start with multimodal immunotherapy

Antitumor strategy
Surgery (→ R(C)T + CT)  Multimodal immunotherapy

Personalized medicine for cancer patients
"Personalized" in three Dimensions!

1. Tumor antigens  2. Immune system  3. Combination therapy

Tumor and host and their interaction are dynamic processes