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Individualized Multimodal Immunotherapy for DIPG: Part of the Game

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Abstract

In 2020 a study, entitled, Addition of multimodal immunotherapy to combination treatment strategies for children with Diffuse Intrinsic Pontine Glioma: A single institution experience was published in Medicines. The text reports the final analysis of 41 children treated with Individualized Multimodal Immunotherapy (IMI) as part of their (combined) treatment schedule. All these children came upon individual request or were referred by the physician to the Immune Oncologic Centre in Köln (www.iozk.de). Since May 2015, the IOZK has the official approval to produce under GMP conditions (DE_NW_04_GMP_2015_0030 and DE_NW_04_GMP_2020_0054) autologous Dendritic Cells (DCs) loaded with autologous tumor antigens and matured in the presence of IL-1b, IL-6 and TNF-a together with GMP-produced Newcastle Disease Virus (NDV). This Advanced Therapy Medicinal Product (ATMP), registered as IO-Vac®, is approved as medicinal product and as experimental medicinal product for use in human (DE_NW-04-MIA-2015-0033 and DE-NW-04-MIA-2020-0017). IO-Vac® is the drug used for active specific immunotherapy. IOZK is a private non-profit organization and delivers, besides 1) IO-Vac® DC vaccines, also 2) Immunogenic Cell Death (ICD) therapies with the Oncolytic Virus (OV) Newcastle Disease Virus (NDV) and modulated electro hyperthermia, eventually inserted in chemotherapy regimens; 3) passive immunotherapy with antibodies, 4) modulatory immunotherapy with antibodies and/or low dose metronomic chemotherapy regimens and/or total body hyperthermia (brain lesions belong to exclusion criteria for this technology) and 5) finally a whole set of complementary medicinal strategies to improve immune reactivity.

Keywords: Immunotherapy • Tumor antigens • Immunogenic cell death • Newcastle disease virus • Oncolytic virus

Introduction

Over the last five years the IOZK developed particular experience in treating children and adults suffering from malignant brain tumors with IMI, preferentially as part of the first line standard of care treatment [1-3]. This unique experience and treatment possibilities were noticed and exchanged by the DIPG parent communities on social media, and created this group of children, 88% of them being treated in IOZK in 2016 and 2017. Because of the novelty of this approach, for both the patients and the IOZK team, interim communications with peers within the Subgroup High Grade Glioma and DIPG from the Brain Tumor Group of the European branch of the International Society of Pediatric Oncology (SIOP-E) have been given: Valencia (12/2015), Amsterdam (10/2017) and Brno (01/2019). Besides, communications were given at the International Society of Pediatric Neuro-oncology and the yearly Rostock Symposia for Tumor Immunology and Brain Tumor Research in Pediatrics, and Minden Symposia for Experimental Neurooncology. The IOZK team had engaged to make a full report of the observations and scientific retrospective analysis of the data [1].

Literature Review

The concept of IMI is a complex combination of ICD therapy and active immunization with IO-Vac®. The mechanism behind and its rationale is meanwhile described in the literature [4]. ICD therapy is performed by intravenous bolus injections of NDV prior to 40-50 minute sessions of local modulated electrohyperthermia. The goal is to kill tumor cells, and change the tumor microenvironment so that danger signals are locally present and the immune system becomes alarmed. This ICD therapy is given for 5 consecutive days. Autologous immature DCs, differentiated ex vivo out of patient-derived monocytes during these 5 days of ICD therapy, are then loaded with ICD therapy-induced serum-derived antigenic extracellular microvesicles and apoptotic bodies. After loading, maturation of loaded DCs is realized in the presence of maturation cocktail and NDV. At day 8 of the culture, IO-Vac® is harvested, GMP-related quality controls are performed, the vaccine is injected intradermally and a sixth ICD therapy is given. The proof of principle to induce a tumor-specific anti-cancer immune response against cancer-specific epitopes using this technology has been demonstrated for GBM [3]. The IOZK generally foresees two such 8-day vaccination cycles with three weeks interval, after which a maintenance immunotherapy is initiated with consecutive blocks of 5 days ICD therapy. In case maintenance chemotherapy was foreseen after the radiotherapy for a DIPG patient, the chemotherapy was combined with ICD therapy, and full vaccination cycles were postponed till after the chemo-ICD-therapy according to a schedule published earlier [2].

DIPG remains in the first place a clinical-radiological diagnosis [5]. In the last ten years, however, a huge success has been reached in unravelling the biology behind DIPG [6-8]. This was only possible because techniques have been developed to do appropriate biopsies [9,10]. By doing this, the diagnostic accuracy of DIPG has been improved, and the clinical-radiological diagnostic criteria have been challenged. The diagnostic entity Diffuse Midline Glioma (DMG) is emerging, covers midline tumors in children and adults connected to the H3K27M-mutant, and is a new entity introduced to High grade glioma in the latest WHO classification [11]. Although the H3K27M tumors form the majority, it means that other diffuse pontine glial tumors still fall under the clinical-radiological DIPG diagnosis but not under the DMG molecular diagnosis. These insights will dominate future clinical trials because the inclusion/exclusion criteria and stratifications during randomizations obligatory have to take these molecular diagnostics derived from biopsied tumors, or the lack of information when no biopsy was performed, into account.

Till now, the pediatric neuro-oncology community did not reach any improvement in overall survival (OS) for DIPG children during the last

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decennia, and the ultimate prognosis of this disease entity remains the worst of all cancer diseases in pediatric oncology [12,13]. All pediatric neuro-oncologists working in the field of DIPG acknowledge that a shift in OS with maintenance of good quality of life is the first and only relevant goal to be reached. That is the reason why we believe that any new treatment strategy and its scientific reporting of results have a huge value for the scientific community. The authors regret the strong repetitive criticism they obtained instead of academic support, although IO-Vac® is an approved ATMP for use in human, although each patient was treated upon own request and after informed consent as "individueller Heilversuch", which is a legal frame for medical treatment in Germany, and although interim retrospective analyses within scientific meetings were repetitively presented and discussed.

Several major barriers have to be crossed for treating DIPG. The particular location in the brain and the blood brain barrier remain major challenges for drug delivery [14]. Several strategies to overcome this barrier are under development, like Convection-Enhanced Delivery [15-17]. A second major barrier is the tumor micro-environment, which is not only an anatomical but also a functional barrier. Only recently, the tumor micro-environment of early disease has been focus of research [18,19]. Surprising data came out. There is no accumulation of macrophages nor T cell infiltration. There is no upregulation of PDL1 on tumor cells. There is no increase of TGF-beta. There is no M2 polarization of macrophages. NK cells can lyse DIPG cell cultures. These findings show a complete different situation as observed in glioblastoma multiforme. These findings, however, seem to be contradictory to the clinical reality of edema noticed on T2 MRI images suggesting fluid accumulation, still hypothesized to be due to local inflammation and treatable with steroids. It should be noticed that a recurrent point mutation in the histone-3 gene (H3F3A) causes an amino acid change from lysine to methionine at position 27 (K27M) resulting in an immunogenic epitope for which peptides in the context of HLA A*0201 are already identified [20-23]. No spontaneous T cell reactivity against this foreign epitope is, however, expected because of lack of appropriate danger signals to initiate an immune response. The specific tumor micro-environment and the lack of danger signals might explain the "cold" milieu without T cell infiltration.

If we want to change the fate of children suffering from DIPG, we should consider the interaction between all these elements mentioned above and the treatments we give. Till now, most treatments rely on a strong anti-cancer focus: irradiation as first gold standard strategy aims to kill tumor cells, without or with chemotherapy [24,25], or targeted therapy based on molecular diagnostics [26-28] or DIPG disease characteristics [29,30]. With these treatments we negatively influence the balance between the tumor and the immune system. The evolution towards necrotic areas and contrast ring enhancement is not hindered at all, at maximum in some cases postponed a bit. The re-occurring edema at that time of disease evolution is likely favouring further migration and invasion of tumor cells that become insensitive for any anti-cancer treatment. Since some years, the paradigm about radiotherapy is allowed to change by the pediatric neuro-oncology community and novel insights to give radiotherapy with different dose and frequency is emerging [31]. It is not excluded that the changed radiotherapy modalities can have a different influence on the tumor micro-environment as compared to the earlier standard schedule and dose, thereby supporting tumor-specific immunity [32]. Besides radiotherapy, other agents can be used as inducers of ICD of tumor cells, thereby changing the tumor micro-environment and triggering an immune response [33-35]. In this domain, the role of OVs is focus of research, and early clinical data on the safety and efficacy of several OVs like NDV [36,37] and genetically engineered tumor-selective adenovirus [38,39] emerge for treatment of DIPG. We use also modulated electrohyperthermia, of which the potency to induce ICD has been demonstrated in preclinical models [40] and clinical contexts [41]. We gave for these children a safe dose of 40 Watt for 40 minutes, which was feasible for all children treated, and which give space for dose increase when considering the loss of specific absorbance rate in connection to the distance. With these combined ICD strategies, we aimed to change the tumor micro-environment so that T cells, activated after injection of IO-Vac® DC vaccines can reach the tumor cells. ICD-inducing regimes form the bridge between the exclusive anti-cancer strategies, mostly blocking the immune system, and the immunotherapy strategies, relying on an anti-cancer functioning immune system. In the search to optimize combinations one can consider to combine anti-cancer targeted therapies with immunotherapy as long as the former do not affect the immune functioning (like it is the case with everolimus). At the individual patient level, the functioning of the immune system can be monitored when using targeted therapies like erlotinib, dasatinib, ONC201, or others. In general oncology a potential gain in long-term OS when using the combination of targeted therapy with immunotherapy has already been suggested more than five years ago [42].

Our report describes that IMI was feasible for these 41 children, coming from 16 different countries, and that no major IMI-related adverse reactions were noticed. We are aware of one other DC vaccine report that also points the safety of DC vaccination in children with DIPG [43]. Although our report was a retrospective analysis without control group, the Kaplan Meier analysis of Overall Survival (OS) suggests a meaningful improvement towards a longer OS as compared to published OS data from DIPG children with comparable clinical and radiological risk profiles. When patients received IMI in connection to first-line treatment, we observed a median OS of 14.4 months, with a 1-year OS of 64.3% (CI95%: +14.6, -20.5) and a 2-year OS of 10.7% (CI95%: +14.3, -8.0) with the longest OS of 38 months. When compared to historical OS data for comparable clinical risk profiles, the observed OS seems to be shifted in comparison with the OS of the intermediate risk group (9.7 months) and the high risk group (7 months) [44]. Of note, patients treated with IMI at time of progression after the first line treatment had a median OS calculated from diagnosis of 9.1 month. Whereas the clinical profile of the children, the feasibility to travel and the persistence of the parents was equal for both the group of DIPG children treated with IMI as part of first line standard of care treatment and the group of DIPG children treated with IMI at time of disease progression after first line treatment, the addition of IMI to the first line treatment resulted in a significant improvement of progression-free survival and a clear trend for improvement of the median OS, pointing the importance to add IMI to the first line treatment.

The connection of IMI to the first line treatment creates a glimpse of hope, and invites further prospective clinical research. However, the design of randomized controlled clinical trials (RCTs) will be extremely challenging, and faces similar problems as depicted for immunotherapy RCTs for glioblastoma [3]. Each patient should be treated with a personalized approach. Clinical trial designs have to take into account not only clinical risk factors, but also tumor-related molecular differences or lack of data when no biopsy is performed, and, last but not least, host-related factors, like the immune profile in blood and tumor microenvironment, change of immune functioning after radio(chemo)therapy and need of steroids. On top of that, dynamic changes during the course of DIPG should be intensively studied as it might point fixed protocol-medicine as completely inappropriate for a dynamic fast changing disease entity, similar as for other brain malignancies [3]. The potential diagnostic and monitoring value of serial liquid biopsies should urgently be investigated and validated for this purpose [45-47].

Conclusion

The extension of the existing DIPG registry [48] with data on the dynamics of the disease and with clinical and laboratory data related to IMI is a first step in getting more insight and knowledge on the additional value of IMI within a complex combined and more and more individualized treatment strategy for children with DIPG. Even when RCTs are not possible anymore, at least a cost-effectiveness model can be developed. In case we can demonstrate in cost-effectiveness models the additional value of IMI as

part of individualized combined treatments to improve OS with good quality of life, the scientific and general community has to make IMI accessible for all children with DIPG within their national health organization. The report for which this commentary was written, illustrates that only a few centers should specialize into delivering IMI for DIPG so that general implementation can happen in a controlled way with continuous further monitoring of effectiveness and quality.

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