Immunotherapy and the Immune Infiltrate in Pediatric Brain Tumors: An Illustration and Review of the Unique Challenges Facing Immunotherapy for Pediatric Oncology

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Abstract

Immunotherapy for pediatric oncology is a robust and prolific area of active research and has changed the face of treatment for some cancers, such as, B cell acute lymphoblastic leukemia (ALL) and neuroblastoma. However, the field faces challenges and hurdles unique to the pediatric population especially in the area of neuro-oncology. Here, clinicians face challenges of using immunotherapy for tumors with some of the lowest mutational burdens in sensitive areas of the brain where surgical intervention is limited and significant immune infiltration is poorly tolerated. Here, we review the current knowledge of the interplay between the immune system and pediatric brain tumors, current clinical trials enrolling patients with pediatric brain tumors, and the challenges unique to this area of research. Early phase clinical trials in pediatric neuro-oncology are plentiful given the rarity of these tumors and efficacy and safety is still to be determined.

Keywords

Immunotherapy, Pediatric brain tumors, Immune infiltrate, Pseudo-progression, Checkpoint blockade, Vaccine, Chimeric antigen receptor (CAR) T cell

Introduction

Immunotherapy for pediatric oncology is a robust and prolific area of active research and has changed the face of treatment in such cancers as neuroblastoma and the hematologic malignancies. Neuroblastoma is the most common extra-cranial solid tumor in childhood. It originates in the adrenal medulla and paraspinal or periaortic regions where the sympathetic nervous system is present. The Children’s oncology group (COG) conducted a phase III trial (ANBL0931) evaluating the efficacy of ch14.18, a monoclonal antibody to tumor-associated disialoganglioside (GD2) in combination with alternating granulocyte-macrophage colony-stimulating factor (GM-CSF) or interleukin-2 (IL-2) [1]. GD2 is present on the majority of neuroblastoma tumor cells even in heterogeneous tumors and is present on only a limited spectrum of normal cells including peripheral pain fibers [2]. The Fc portion of ch14.18 binds the Fc receptor of monocytes, macrophages, neutrophils, and natural killer cells to stimulate tumor cell lysis via antigen-dependent cell-mediated cytotoxicity (ADCC) and also triggers complement-dependent cytotoxicity (CDC). In a COG study (ANBL0032), patients with high risk neuroblastoma were randomized after completion of chemotherapy, autologous stem cell transplant, and radiation to standard therapy with isotretinoin versus treatment with isotretinoin plus anti-GD2 combined with GM-CSF alternating with IL-2 [3]. The experimental arm was found to be superior with an 2 year event free survival (EFS) of 66% ± 5% vs. 46% ± 5% (p = 0.01) and overall survival (OS) 86% ± 4% vs. 75% ± 5% (p = 0.02). Isotretinoin itself is known to have distinct effects on immune system including changing the levels of natural killer (NK) cells and alterations in the innate immune system [4,5]. Immunotherapy improved outcomes for this very high risk group of patients and is now part of the standard of care.

In the area of hematologic malignancies, mature B cell lymphoma patients benefited from the addition

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of rituximab being added to the standard LMB-96 chemotherapy backbone in the COG study ANHL1131 [6]. Rituximab is a genetically engineered chimeric murine/humanized monoclonal IgG1 kappa antibody directed against the CD20 antigen. In the interim analysis for this study, 1 year EFS was 81.5% in the control arm compared to 94.2% in the rituximab arm. Although the primary endpoint of EFS did not cross the pre-specified efficacy boundary, conditional power analysis predicted a high likelihood of a positive study. As a result, the Independent data safety monitoring committee (IDSMC) recommended discontinuation of randomization and that all children with high risk B cell lymphoma received the LMB chemotherapy backbone plus an additional 6 injections of Rituximab.

There has also been success seen in pediatric oncology for adoptive cellular immunotherapy. Chimeric antigen receptor (CAR) T cells combine antigen binding and recognition with T cell activating functions in a single molecule. The chimeric antigen receptor is engineered to have arbitrary specificity on an immune effector cell. As a therapeutic agent, the specificity is typically to a cancer-specific antigen. In recurrent or refractory B cell ALL, CAR T cells directed against CD19+ leukemia cells resulted in an 80% overall survival at 1 year and were found to persist up to 1 year [7]. The relapse free rate was 75% at 6 months and 64% at 12 months, an unprecedented result for a patient group that is heavily pre-treated. Overall survival was 89% at 6 months and 79% at 12 months. CD19 CAR T cell therapy is now being considered for incorporation into the next children’s oncology group (COG) study for ALL in the setting of positive minimal residual disease after consolidation.

Despite these examples of successes of immunotherapy, there are also unique challenges and hurdles facing utilization of immunotherapy in pediatric oncology. Generally, pediatric tumors may be less antigenic than many adult cancers, carrying much lower mutational loads compared to their adult counterparts [8]. For instance, rhabdoid tumors, seen in the kidneys as well as in the brain, possess only a solitary genetic alteration, a mutation in the SWI/SNF related, matrix associated, actin dependent regulator of chromatin, subfamily B, member 1 (SMARCB1) gene. We also know that the pediatric immune system evolves from a neonate to an older child with an initially immature innate and adaptive immune system that acquires memory over time [9]. This may result in variations in the immune response to tumors not only when compared to adults, but even throughout childhood development. There are practical differences in the management of immunotherapy for pediatric tumors as well. For instance, in the area of pediatric brain tumors, two-thirds of the tumors exist in the posterior fossa while only 15% of adult brain tumors occur in this space. The posterior fossa is an area where pseudoprogression or tumor inflammation related to immunotherapy can result in significant clinical issues, such as hydrocephalus and increased intracranial pressure as well as brainstem dysfunction including apnea or the inability to swallow. However, pediatric patients have decades to accumulate long term sequelae from traditional therapies such as radiation and chemotherapy and may serve to benefit the most from therapies that harness their own immune system into a cytotoxic therapeutic. Here, we will review the case of pediatric brain tumors to illustrate some of the challenges facing immunotherapy for pediatric oncology.

The Immune Infiltrate

Much is known about the immune infiltrate in adult gliomas. Research has confirmed that there is indeed immune trafficking to the brain and evaluation of adult glioma immune infiltrate has shown a significant difference between the infiltrate of low grade versus high grade glioma [10]. High grade gliomas have evidence of a more robust immune response with more natural killer (NK) cells and a higher T cell infiltrate and CD8: CD4 T cell ratio but also a more immunosuppressed phenotype with more infiltrating regulatory T cells and macrophages of the M2 subtype. The presence of an increased immune infiltrate, especially CD8 T cells, has also been associated with improved prognosis in adult gliomas [11]. Multiple immune escape mechanisms within the innate and adaptive immune systems have also been identified [12]. In contrast, little is known about the immune infiltrate in pediatric tumors and how this compares to their adult counterparts.

In a previous study, the immune infiltrate of pediatric brain tumors was evaluated using multicolor FACS and gene expression microarray on disaggregated tumor tissue [13,14]. In this study, ependymomas and pilocytic astrocytomas showed a larger myeloid infiltrate and a more activated phenotype with HLADR and CD64 positivity. Higher grade lesions, such as, medulloblastoma and glioblastoma had a smaller T cell infiltrate and a larger percentage of memory T cells. From this study, the authors concluded that low grade tumors may benefit from vaccine therapies given the presence of a pre-existent immune infiltrate while high grade tumors like medulloblastoma and glioblastoma may benefit from checkpoint blockade to counteract the suppressive immune microenvironment [14].

In another study, FACS analysis was conducted on 22 fresh pediatric brain tumors and corresponding peripheral blood samples. Immunohistochemistry for major immune markers was run on an additional 89 pediatric brain tumor samples [15]. The immune infiltrate was dissimilar to that reported for adult gliomas. Low grade gliomas had a higher T cell infiltrate than high grade gliomas. This was confirmed with T cell receptor sequencing of the TCR variable beta chain sequencing and clonality analysis.
Unlike in adult studies, in the pediatric analysis, there was no statistical correlation between immune markers for the CD45 immune subset, CD8 T cells, CD20 B cells, or FoxP3+ regulatory T cells and survival, although this could be due to lower sample numbers compared to adult studies [15]. Mutational load in this series of pediatric brain tumors was low overall but did correlate with the presence of CD8 effector memory T cells, activated memory T cells, activated CD20 B cells, and regulatory T cells as determined by FACS immune subsets. This suggests that low mutational burden could, in fact, be impacting the immunogenicity of these tumors.

Overall, the analysis of the immune infiltrate in pediatric brain tumor studies demonstrated disparate results from the adult data, with less impact on prognosis but did have a positive correlation with mutational load. Future studies in pediatric oncology should focus on understanding the interplay between pediatric tumors and the immune system and how this may implicate specific immunotherapies. Extrapolation from adult data should be used with caution.

**Clinical Trials in Immunotherapy**

Recent clinical trials for immunotherapy in pediatric brain tumors span the gamut of immunotherapy subtypes (Table 1). In the area of vaccines, the Pacific

<table>
<thead>
<tr>
<th>Recent clinical trials: Immunotherapy for pediatric brain tumors Type of immunotherapy</th>
<th>Clinical trials.gov identifier</th>
<th>Lead institution/Consortium</th>
<th>Investigational agent</th>
<th>Eligible tumor type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vaccine</td>
<td>NCT02960230</td>
<td>University of california, San francisco (PNOC)</td>
<td>H3.3K27M peptide vaccine</td>
<td>HLA-A201+ children with newly diagnosed DIPG and H3.3K27M positive glioma</td>
</tr>
<tr>
<td></td>
<td>NCT01130077</td>
<td>University of pittsburgh</td>
<td>Glioma-associated antigen vaccine (EphA2, IL-13Rα2, survivin)</td>
<td>HLA-A2+ children with DIPG or recurrent or High grade glioma</td>
</tr>
<tr>
<td></td>
<td>NCT01808820</td>
<td>University of miami (HGG Immuno Group)</td>
<td>Tumor lysate pulsed dendritic cell vaccine + Imiquimod</td>
<td>High grade glioma</td>
</tr>
<tr>
<td></td>
<td>NCT02722512</td>
<td>Lurie children’s hospital of chicago</td>
<td>Heat shock protein peptide complex-96 (HSPPC-96) vaccine</td>
<td>Newly diagnosed or Recurrent high grade glioma</td>
</tr>
<tr>
<td></td>
<td>NCT03068832</td>
<td>Washington university</td>
<td>Neo-epitope personalized synthetic long peptide vaccine</td>
<td>Recurrent malignant CNS tumors</td>
</tr>
<tr>
<td>CAR T cell</td>
<td>NCT03500991</td>
<td>Seattle children’s hospital</td>
<td>HER2-specific CAR T cell</td>
<td>HER2-positive recurrent or Refractory CNS tumors</td>
</tr>
<tr>
<td></td>
<td>NCT02208362</td>
<td>City of hope medical center</td>
<td>IL13Rα2-specific CAR T cell</td>
<td>Recurrent or Refractory high grade glioma</td>
</tr>
<tr>
<td>Checkpoint blockade</td>
<td>NCT02502708</td>
<td>Children’s healthcare of atlanta</td>
<td>IDO pathway inhibitor plus indoximod and Temozolomide</td>
<td>Progressive malignant brain tumors (including DIPG)</td>
</tr>
<tr>
<td></td>
<td>NCT02359565</td>
<td>National cancer institute/Children’s national medical center (PBTC)</td>
<td>Pembrolizumab</td>
<td>Recurrent, refractory high grade glioma, DIPG, Hypermutated tumors, Ependymoma, Medulloblastoma</td>
</tr>
<tr>
<td></td>
<td>NCT02992964</td>
<td>The hospital for Sick children</td>
<td>Nivolumab</td>
<td>Hypermucant tumors</td>
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<tr>
<td></td>
<td>NCT03130959</td>
<td>Bristol meyers squibb</td>
<td>Nivolumab, Ipilimumab</td>
<td>High grade CNS malignancies</td>
</tr>
<tr>
<td>Viral gene therapy</td>
<td>NCT00634231</td>
<td>Dana farber cancer institute</td>
<td>ADV-4k + Prodrug therapy in combination with radiation</td>
<td>Malignant glioma (WHO grade III or IV); Recurrent ependymoma</td>
</tr>
<tr>
<td></td>
<td>NCT03330197</td>
<td>Ziopharm</td>
<td>Ad-RTS-hIL-12 + Veledimex</td>
<td>DIPG and Recurrent malignant brain tumors</td>
</tr>
<tr>
<td>Viral targets</td>
<td>NCT03299309</td>
<td>Duke university</td>
<td>PEP-CMV vaccine (human pp65 and CMV glycoprotein B + KLH)</td>
<td>Recurrent medulloblastoma and Malignant glioma</td>
</tr>
</tbody>
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pediatric neuro-oncology consortium (PNOC) has an open phase I study for a H3.3K27M peptide vaccine for HLA-A2+ children with diffuse intrinsic pontine glioma and high grade glioma (NCT02960230). Diffuse intrinsic pontine glioma (DIPG) is an expandible gliotum of the pons most commonly seen in children 5 to 9-years-old [16]. Although this tumor only occurs in around 200 cases per year, it is the focus of many clinical trials given its dismal prognosis of < 1% 5 year overall survival and median overall survival of 11 months. Histone 3.3 and 3.1 mutations are present in over 80% of DIPG and 30% of glioblastoma [17]. The most common mutation causes a lysine to methionine switch at position 27 in one allele of H3F3A. This mutation re-programs the epigenetic landscape resulting in alterations in gene expression which then drive tumorigenesis. Epigenetic regulation of gene expression is a notoriously difficult target for treatment and immunotherapy is one avenue researchers are pursuing to address this.

Other vaccine trials in pediatric neuro-oncology include a glioma-associated antigen vaccine in HLA-A2+ children with DIPG or recurrent low or high grade tumors (NCT01130077) and a tumor lysate pulsed dendritic cell vaccine for high grade glioma (NCT01808820). A heat shock protein vaccine (HSPPC-96) (NCT02722512) and synthetic long peptide personalized neo-epitope vaccine (NCT03068832) are also being conducted in pediatrics.

In the area of adoptive cellular immunotherapy, a chimeric antigen receptor (CAR) T cell with specificity to HER2 is available in a phase I clinical trial for recurrent HER2-positive recurrent or refractory pediatric CNS tumors (NCT03500991). This trial is evaluating the safety and efficacy of autologous CD4 and CD8 T cells transduced with a lentivirus to express a HER2-specific CAR. The CAR T cell product is then administered directly into the tumor resection cavity or ventricular system using an indwelling catheter. Patients can receive anywhere from two to six courses of CAR T cell infusion depending on how they tolerate the therapy. In another open trial, an IL13Ra2-specific, 41BB costimulatory, CAR T cell product is administered weekly for three weeks into the intratumoral or intraventricular catheter (NCT02208362). Preliminary evidence of antitumor activity of an anti-di-sialoganglioside (GD2) CAR T cell in H3.3K27M midline glioma orthotopic xenograft models will also likely lead to a new CAR T cell trial for DIPG and H3.3K27M mutant tumors [18]. Xenograft models for these midline tumors revealed significant inflammation at the site of the tumor which did result in lethal hydrocephalus in a few of the animals. Investigators suggest neurointensive care management will be essential in the upcoming in-human trial [15].

Checkpoint inhibition has also been an active area of research for pediatric brain tumors. The Pediatric brain tumor consortium (PBTC) has developed a phase I trial evaluating the safety and feasibility pembrolizumab for recurrent or progressive DIPGs, high grade gliomas, hypermutant tumors, ependymoma, and medulloblastoma (NCT02359565). Early data from this trial revealed challenges in management of peritumoral inflammation and pseudoprogession for tumors located in the brain-stem and posterior fossa, leading to subsequent trial design alterations in order to maximize the safety of this approach. The results of CheckMate-143 for adult glioblastoma revealed tolerability and early efficacy data of the combination of nivolumab and ipilimumab (PD1 and CTLA4 inhibition, respectively) [19,20]. This trial is also now open to pediatric high grade CNS malignancies on CheckMate-908 (NCT03130959).

Viral based gene therapies have also expanded into pediatric neuro-oncology. Therapeutic IL-12 has been under investigation because of IL-12’s ability to bind IL-12 receptors on natural killer (NK) cells and T cells and its ability to polarize T cell differentiation towards type 1 helper T cells (Th1) and interference with regulatory T cell differentiation [21]. Unfortunately, it is difficult to use therapeutically because it is unstable by itself and has a short half-life. Ad-RTS-hIL-12 is a viral product that uses a replication incompetent adenoviral vector delivery of the IL-12 gene under regulation of an activator molecule ligand. In adults, the gene therapy was found to be tolerable with a reasonable safety profile [23]. This trial is also open for pediatric patients with DIPG or recurrent malignant brain tumors (NCT03330197). Similarly, a trial using an adenoviral vector containing the herpes simplex virus thymidine kinase gene (ADV-tk) plus prodrug, valacyclovir, is being tried in combination with radiation and temozolomide in pediatric brain tumors (NCT00634231). This therapy works by the phosphorylation of the valacyclovir by the HSV-tk converting the drug into nucleotide analogs which are toxic to dividing or actively repairing cells [22]. This effect is thought to be potentiated by the concurrent use of DNA-damaging therapy, such as radiation and chemotherapy and has been safely delivered in adults [24].
In the area of oncolytic viruses, PNOC has opened a phase I study of an attenuated modified measles virus (MV-NIS) for the treatment of recurrent medulloblastoma and atypical teratoid rhabdoid tumor (ATRT) (NCT02962167). This oncolytic virus contains a human thyroidal sodium iodide symporter (NIS) that allows evaluation of the distribution and cytotoxic effect of the measles virus on SPECT imaging [25]. The MV-NIS is injected into the tumor bed or subarachnoid space. Oncolytic viruses work by taking advantage of selective viral replication and killing in cancer cells that do not possess the cellular repair mechanisms of normal cells [26]. This selective killing also induces a systemic anti-tumor immune response. A survival benefit has been observed with the oncolytic virus polio/rhinovirus recombinant (PVSRIPO) in treatment of adult glioblastoma and is being accelerated for FDA approval [27].

Oncolytic poliovirus is administered intracerebrally by convection-enhanced delivery (CED) and is now in an open phase 1b trial for children with recurrent WHO III or IV malignant glioma (NCT03043391). Immunotherapy trials in pediatric neuro-oncology are not limited to the United States. In Spain, a Phase I trial for DNX-2401, an oncolytic virus targeting tumor cells with abnormalities in the RB pathway, is open for patients with DIPG (NCT03178032). The virus will be injected through a catheter using the same trajectory as the initial biopsy and the virus will infect cells through integrins which are abundant in gliomas. If DNX-2401 is safe in children, this trial will be moved to a multi-institutional trial in Europe.

As many of these new and exciting therapies remain in Phase I or I/II studies without published data, it is difficult to assess what immunotherapy strategies are the most advantageous or how they compare against each other in terms of efficacy. Based on previous research, monotherapy with checkpoint blockade appears to be most effective against tumors with high mutational burden [28-30]. This suggests pediatric brain tumors may require combination immunotherapy that also ignites antigen presentation and recognition, such as vaccine therapy in combination with checkpoint blockade. In a previously reported phase I trial for glioma-associated antigen (GAA) epitope peptide vaccines in HLA-A2 positive children with newly diagnosed brainstem glioma and high-grade glioma, all children had positive enzyme-linked immunosorbent spot analysis for anti-GAA immune response [31]. Of 26 children enrolled, 19 patients had stable disease, 2 had partial responses, 1 had a minor response, and 2 had prolonged disease-free status after surgical resection. In a pilot study evaluating tumor lysate pulsed dendritic cell vaccine in 3 pediatric patients with high-grade glioma, moderate cytokine profile changes were observed in peripheral blood of patients and, in one patient with recurrent disease post vaccination, limited immune infiltrate was seen in resected tissue [32]. Another effective strategy may be immunotherapies that utilize antigen exposure during radiation. During radiation therapy, tumor antigens are exposed and processed by antigen presenting cells for presentation [33,34]. If immunotherapy treatment aimed at expanding the immune response can be given in close proximity to the radiation therapy, it may result in more robust immune-mediated cytolytic activity. Also, CAR T cells have been promising in preclinical models and also bypass the need for antigen presentation and T cell activation [18]. In tumors with low mutational burden, this may be an effective strategy. In a patient-derived diffuse midline glioma orthotopic xenograft model, a GD2-targeted CAR T cell resulted in complete responses in all five models with only small numbers of residual H3.K27M+ tumor cells remaining [18]. This treatment will soon enter a phase I clinical trial.

Overall, immunotherapy-based clinical trials for pediatric brain tumors span multiple modalities including checkpoint inhibition, vaccine therapy, adoptive cellular immunotherapy, and virally-mediated immunotherapies. This wide breadth of trial activity highlights the need for better treatments for pediatric malignant brain tumors and emphasizes the excitement around immunotherapy for pediatric patients who face a multitude of long term sequelae of current radiotherapy and chemotherapy regimens.

Challenges Facing Immunotherapy for Pediatric Neuro-Oncology

The challenge of pseudoprogression is not unique to pediatric neuro-oncology. Experience from immunotherapy trials for adult brain tumors revealed a need for specific disease assessment criteria unique to this field of research. As clinicians and radiologists attempted to distinguish tumor related inflammation from tumor growth on MRI’s for patients on immunotherapy trials, they realized the standard response assessment criteria in neuro-oncology (RANO) was insufficient. Patients who are experiencing a positive immune response from treatment and subsequent inflammation at the tumor site would be typically labeled ‘progressive disease’ based on strict RANO criteria. A new schematic was developed known as the immunotherapy response assessment criteria for neuro-oncology (iRANO) [35]. It incorporates repeated MRI scans for patients where pseudoprogression versus true progression is unclear and they are within the first 6 months of initiation of immunotherapy. It also adds the use of particular MRI images like T2 FLAIR to try to tease out this issue of pseudoprogression as well.

The iRANO criteria are useful in evaluation of supratentorial lesions and in the context of minimal clinical decline observed in the setting of pseudoprogression. However, in pediatrics most of the tumors being evaluated are in very sensitive areas of the brain, namely the posterior fossa, so significant symptomatology related to pseudoprogression is not uncommon and can require
early initiation of steroids or discontinuation of therapy. Swelling of a posterior fossa tumor can result in hydrocephalus via compression of the 4th ventricle causing the patient to experience headache, nausea, and vomiting. Peritumoral swelling of brainstem tumors can result in motor dysfunction and cranial nerve deficits impairing swallowing and even leading to apnea and death. In the open PBTC trial for pembrolizumab, initial signs of progression resulted in temporary closure in order to tease out the impact of possible pseudoprogression in this patient population. Due to the unique mechanism of action for immunotherapy, traditional measures of progression, including MRI ‘growth’ or appearance of new obvious disease sites with or without subsequent clinical deterioration, may not be reliable. Novel imaging modalities such as ferumoxytrol imaging, novel PET isotopes, and spectroscopy are being investigated in order to more clearly delineate this difference.

Steroid use for pediatric brain tumors is very common and is exacerbated by treatment with radiation. The goal of most immunotherapy trials is to limit or decrease dosing to a physiologic steroid level. Some clinical trials have required less than 0.5 mg/kg/day of steroids, although even that restriction likely impairs the efficacy of immunotherapy [36]. For example, patients with diffuse intrinsic pontine glioma (DIPG) often require initiation of steroids at diagnosis for cranial nerve deficits and most receive dexamethasone during radiation treatment. It is sometimes impossible to wean steroid doses due to significant symptoms, which may be worsened by initiation of immunotherapy. This presents unique ethical considerations when testing immunotherapy. For instance, should invasive supportive measures, such as, NG tubes or mechanical ventilation be undertaken for patients receiving phase I experimental agents? When can a diagnosis of pseudoprogression be made, and how can parents be advised when making decisions surrounding heroic measures, such as intubation or resuscitation? How do we view these same decisions in patients with DIPG who possess <1% chance of survival at 5 years?

The location of the majority of pediatric brain tumors makes the use of immunotherapy a challenge both in terms of pseudoprogression and the use of steroids for symptom management. For those designing clinical trials in immunotherapy for pediatric brain tumors, there is a tight balance between patient safety and accurate evaluation of efficacy of these therapies.

Conclusions

Immunotherapy for pediatric malignancies has had recent successes in acute leukemia and neuroblastoma. However, future immunotherapy research in pediatric oncology will need to address the challenges of low mutational load tumors and potentially limited immunogenicity, differences in pediatric and adult immune infiltrate, and nuances to management of toxicity of immunotherapy in children. The applications in pediatric neuro-oncology continue to present additional obstacles involving appropriate clinical trial design and management of pseudoprogression and steroid use, although the refinement of iRANO and accumulation of experience with immunotherapy in the central nervous system hold hope for the future.

References


