The value of immunotherapy in pediatric leukemia and lymphoma

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Summary Leukemia and lymphoma are a leading cause of cancer-related mortality in children and the prognosis for patients with relapsed or refractory disease remains poor. Standard therapies are associated with a wide array of acute and long-term toxicities. Immunotherapy is changing the treatment landscape for pediatric leukemia and lymphoma patients and has advanced at a tremendous pace over the last decade. Immunotherapies are thought to exhibit fewer long-term toxicities than chemotherapy and radiation, which makes it very appealing in the field of pediatrics. These novel therapeutic concepts may overcome resistance to and decrease side effects of standard therapy. Many therapies are currently being investigated, from immunomodulatory agents to adoptive cell therapy, bispecific T-cell engagers, oncolytic virotherapy, and checkpoint inhibition. A critical challenge that must be overcome is the identification of biomarker(s) to identify patients who would benefit from immunotherapy.

Keywords Pediatric leukemia and lymphoma · Immunotherapy · Innovative treatments

Introduction

The treatment of pediatric leukemia and lymphoma, impacting more than 30% of childhood cancer patients, has undergone substantial progress over the last decade [1–4]. Despite this, leukemia remains

a leading cause of pediatric cancer-related mortality and the prognosis for individuals with relapsed or refractory disease remains poor. Standard therapies are associated with a wide array of acute and long-term toxicities and further treatment intensification may not be tolerable or beneficial, necessitating novel targeted approaches. While most immunotherapy-related studies have focused on adult malignancies, a handful of these therapies have also recently found success in the field of pediatrics. Immunotherapy is changing the treatment landscape for pediatric leukemia and lymphoma patients and has advanced at a tremendous pace over the last decade.

However, the concept of immunotherapy for cancer is not new and has been documented since the 19th century [5–7]. The immune system is a highly complex organization of cells and proteins that cooperate to eliminate infections while maintaining tolerance against self. The complex interplay between the patient's immune system and cancer is also termed 'immunoediting' and includes immune surveillance, immune cell infiltration, and tumor cytolysis [8–11]. Immunoediting itself can further be divided in three different phases: elimination, equilibrium, and escape [12]. Immunotherapies aim to counteract the escape phase and reinvigorate the patient's immune system to recognize and eliminate cancer cells. These approaches may overcome resistance to and decrease side effects of standard therapy. Many therapies are currently being investigated, from immunomodulatory agents to adoptive cell therapy, bispecific T-cell engagers, oncolytic virotherapy, and checkpoint inhibition. In pediatric leukemia and lymphoma antibody therapy, antibody–drug conjugates (ADC), bi-specific T-cell engagers (BiTE), and chimeric antigen receptor (CAR) T cells have shown most promising and will be discussed in detail and are summarized in Fig. 1.

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Antibody and Antibody-like therapy

Adoptive Therapies

Immune Checkpoint Inhibitors

Fig. 1 Schematic representation of immunotherapy options in pediatric leukemia and lymphoma. Antibody and antibody-like therapy (left) is illustrated by the examples of rituximab, blinatumomab, and inotuzumab. For adoptive therapies

chimeric antigen receptor (CAR) T cell therapy is shown (top right) and checkpoint inhibitor therapy is shown with the example of PD1-checkpoint therapy (nivolumab; bottom right). The figure was generated using Biorender

Antibody and antibody-like therapy

Antibody therapy has been used in many pediatric cancer types and has shown much promise. Monoclonal antibodies (mAbs) attach to a specific tumor surface antigen resulting in activation of NK cells and macrophages via Fc-receptor binding. Once activated, these cells release cytotoxic granules to kill the tumor cell in a process called antibody-dependent cellular cytotoxicity [13]. mAbs are tumor-specific instead of patient-specific and can be easily stored without the need for local manufacturing expertise. Rituximab, a CD20-specific mAb, was the first mAb approved for clinical use in 1997 for adults. In pediatric non-Hodgkin lymphoma (NHL) patients, the addition of rituximab to standard chemotherapy increased the 1-year event-free survival (EFS) from 81.5 to 94.2% [14]. Anti-CD22 mAbs have been successfully utilized in both adult and pediatric B-cell acute lymphoblastic leukemia (ALL) [15–17]. Brentuximab vedotin, an anti-CD30 mAb drug conjugate (ADC), was approved by the US Food and Drug Administration (FDA) in 2011 for relapsed or refractory Hodgkin lymphoma (HL) and anaplastic large-cell lymphoma. A higher overall response rate was seen in patients with relapsed/refractory HL who received brentuximab vedotin compared with vinorelbine [18]. In a phase III

Children's Oncology Group study, the combination of brentuximab vedotin with gemcitabine for relapsed HL is being evaluated (NCT01780662).

BiTEs consist of two single-chain variable fragments connected by a flexible linker. They connect and activate T cells with the tumor-specific antigen, where one side binds to the CD3 receptor of the T cell and the other side to the tumor antigen, resulting in the activation of T cells and subsequent cytotoxicity of the tumor cell [19]. Blinatumomab, a CD19/anti-CD3 BiTE, was approved by the FDA in 2017 for the treatment of relapsed or refractory B-cell ALL in the pediatric population after being approved in 2014 for adult patients. Overall survival (OS), remission rates, and EFS were significantly longer or higher in the blinatumomab group compared with standard chemotherapy [20, 21]. Blinatumomab has also been approved for the treatment of minimal residual disease positive B-cell ALL patients.

Allogeneic hematopoietic stem cell transplantation (aHSCT) and adoptive cell therapy

HSCT is the most established and commonly used cellular immunotherapy in cancer care. It is the most potent anti-leukemic therapy in patients with acute

myeloid leukemia and is routinely used with curative intent in patients with intermediate and high/very-high risk disease or at relapse for patients with NHL. Donor T cells, and possibly other immune cells, eliminate residual leukemia cells after prior (radio)chemotherapy. This immune-mediated response is known as graft-versus-leukemia (GvL) [22, 23]. After allo-HSCT, relapse is still a major complication and current evidence suggests that relapse is not due to clonal evolution, but instead to the ability of tumor cells to escape immune control by a variety of mechanisms such as by decreasing human leukocyte antigen (HLA) expression and/or tumor antigens.

The most successful option to overcome this challenge are chimeric antigen receptor T cells (CAR-T) [24]. A chimeric antigen receptor is composed of an extracellular domain with an antigen-binding domain derived from a monoclonal antibody specific for a tumor surface antigen, a spacer domain, a transmembrane domain, and an intracellular signal-transducing chain of the T-cell receptor. CAR-Ts are able to engage a specific antigen without the need of HLA presentation of tumor neoantigens [25]. The most impressive immunotherapy results have come from the CD19 CAR-T therapy in both adult [26, 27] and pediatric patients [28, 29] with chemotherapy resistant B-cell ALL and the CD19 CAR-T therapy (Kymriah®) was approved by the FDA in 2017. However, more CAR-T therapy targets are needed for hematologic malignancies, as illustrated by patients who experience relapse after CD19 CAR-T therapy. Novel CAR-Ts for leukemia and lymphoma patients targeting CD-22 [30, 31], CD30 [32], CD123 [33], and thymic stromal lymphopoietin receptor [34], respectively are currently tested in preclinical and clinical model systems.

Natural killer (NK) cells recognize a target without engaging specific antigens. The concept of utilizing NK cells to destroy tumor cells stems from experiments in murine leukemia models [35] and has been verified in preclinical and clinical trials of adult AML patients [36] and later also pediatric AML patients [37]. Currently, there are only a few clinical trials utilizing NK cell therapy for pediatric hematologic malignancies, as the concept is rather pursued for pediatric solid tumors.

Checkpoint inhibitors

Immune checkpoints are key regulators to prevent auto-immune activity that when stimulated dampen the immune response to an immunologic stimulus. Studies have shown that immunogenic tumors can escape immune surveillance by reducing an oncolytic immune response via expression checkpoint ligands [38]. Two of the most commonly applied checkpoint inhibitors target PD1-PD1-L and the CTLA4-CD80/86 axis [39]. CTLA-4 is expressed on the surface of activated T cells and binds to CD80/86 on dendritic

cells (DCs), leading to deactivation of the T cell [40]. CTLA-4 checkpoint inhibition is widely used for adult solid tumor therapy (e.g., melanoma, lung, and kidney cancers), but only limited data exist for pediatric solid tumor therapy (e.g., metastatic melanoma [41]).

PD-1 is expressed on chronically activated T cells, B cells, DCs, and macrophages. Under physiological circumstances, PD-1 signaling limits the inflammatory immune response to prevent autoimmunity [38]. Experience in pediatric hematological malignancies is limited to Hodgkin's disease and non-Hodgkin's lymphoma as in the ongoing Children's Oncology Group (COG) protocol ADVL1412 [42]. In March 2017, the FDA approved pembrolizumab, the anti-PD1 antibody, for the treatment of adults and children with refractory classic HL or those who relapsed after three or more prior treatments [43].

One of the hypotheses to explain the differences in response rates between certain adult cancers compared with pediatric cancers is the mutational load or lack thereof. As pediatric cancers in general do not have a high mutational burden in their tumors, decreased immunogenicity is suspected [44]. One exception involves pediatric patients with biallelic mismatch repair deficiency. These patients have a very high risk of cancer throughout life and their tumors are associated with an exceptionally high mutational burden, even higher than adult cancers. The PD-1 antibody pembrolizumab has been shown efficient for the treatment of mismatch repair deficiency tumors in patients 12 years and older [45].

Limitations and challenges

Despite the promising developments in immunotherapy for adult oncology, fewer successes have been achieved in the pediatric setting. This result may in part be due to the significantly lower mutational load in pediatric cancers, which limits the number of neoantigens for immunotherapies to target. A critical challenge that must be overcome is the identification of biomarker(s) to identify patients who would benefit from immunotherapy. Much research is being focused on which biomarkers will be predictive and prognostic for these patients. Still, immunotherapies are thought to exhibit fewer long-term toxicities than chemotherapy and radiation, which makes it very appealing in the field of pediatrics. With few downsides and the potential for disease cures, immunotherapy in the pediatric population has the potential to move to the front-line of therapeutic options [46].

Although the ultimate contribution of immunotherapies to the treatment and outcome of pediatric cancer patients remains uncertain, the landscape of therapy in the near future is likely to be quite different from traditional surgery, radiation, and chemotherapy.

Take Home Message

The use of immunotherapy for pediatric leukemia and lymphoma patients has been successful in creating durable remissions for multiply relapsed and refractory patients who previously had little chance of cure. The ongoing clinical and preclinical work continues to advance our understanding of these immune-based therapies and will shape the next generation of clinical trials.

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Conflict of interest E. Salzer and A. Attarbaschi declare that they have no competing interests.

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