HHS Public Access

Author manuscript

Expert Rev Clin Immunol. Author manuscript; available in PMC 2022 June 23.

Published in final edited form as:

Expert Rev Clin Immunol. 2020 April ; 16(4): 361–371. doi:10.1080/1744666X.2020.1732819.

Harnessing immunotherapy for pediatric T-cell malignancies

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Abstract

Pediatric T-cell hematologic malignancies are a diverse group of rare cancers. The most common pediatric T-cell malignancies include T-cell acute lymphoblastic leukemia (T-ALL) and anaplastic large cell lymphoma (ALCL). Although the overall survival rates have improved markedly in recent years, children with relapsed T-ALL and ALCL have very low rates of cure and few salvage therapies exist. Current treatment regimens rely on toxic chemotherapies with significant short- and long-term morbidity. Immunotherapies, including antibodies and adoptive cellular therapies, have revolutionized the treatment of B-cell malignancies in pediatrics. The adaptation of these therapies to T-cell malignancies has been slower because of challenges implicit in the design and implementation of immunotherapies for T-cell malignancies, including the potential risks of fratricide, immunosuppression, and graft versus host disease (GVHD). We present a review of current challenges in the development of immunotherapies for T-cell hematologic malignancies, potential solutions and therapies under investigation. We include a particular focus on T-ALL and ALCL. Immunotherapies offer promising strategies to improve outcomes in children with T-cell malignancies, particularly in the setting of relapse. Optimizing efficacy, mitigating toxicity, and safely integrating with conventional therapies are key considerations as immunotherapies are translated into the clinic.

Keywords

T-cell acute lymphoblastic leukemia; anaplastic large cell lymphoma; pediatric cancer; immunotherapy

1. Introduction

Immunotherapy is a revolutionary approach to the treatment of hematologic malignancies which seeks to harness the body's own immune system to target cancer cells. The first

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Reviewer Disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

clinically available immunotherapies were monoclonal antibodies[1]. These agents have been successfully incorporated in to chemotherapy protocols for several decades, however, their efficacy has been somewhat limited[2]. When used for treatment of cancer, monoclonal antibodies work either by direct stimulation via antigen binding, or more commonly, through antibody-dependent cellular cytotoxicity (ADCC)[2]. To optimize the efficacy of monoclonal antibodies several approaches have been developed, including marrying antibodies to chemotherapy agents (antibody drug conjugate; ADC) or leveraging the engagement of T-cells [3,4]. Bispecific T-cell engagers (BITEs) bind to a marker on a malignant cell as well as to endogenous T-cells[4]. The purpose of this approach is to bring T-cells in close proximity to targeted malignant cells and to stimulate endogenous T-cells, in order to optimize tumor cell death[5]. In contrast to antibody directed therapies, adoptive cellular therapies seek to directly harness T-cells to fight cancer cells. An example of adoptive cellular therapies are chimeric antigen receptor T-cells (CAR-T). CAR-T cells are autologous or allogeneic T-cells which have been genetically modified to target a marker on malignant cells[6]. Similar approaches are under investigation, utilizing different types of effector cells. Natural Killer (NK) cell CARs use a chimeric antigen receptor targeting a tumor antigen of interest with an NK-cell as an effector cell[7].

The advantage of CAR-T cells over monoclonal antibodies or other immunotherapies are numerous. For example, CAR-T cells may persist for a longer period of time than antibodies allowing for ongoing tumor surveillance and killing[6]. The potential down-side to this prolonged exposure is a longer period of potential toxicity. Many CAR-T cells also have better CNS penetration than monoclonal antibodies. While this has not been studied extensively, few monoclonal antibodies cross the blood brain barrier (BBB). As an example, the concentrations in the CSF are ~0.7% of plasma levels after treatment with the anti-CD20 monoclonal antibody rituximab[8]. Some CAR-T cell products, in contrast, have been demonstrated to have very good penetration of the BBB.

To date, the majority of immunotherapies that have been successfully implemented in to clinical care have targeted B-cell malignancies[6]. Rituximab is a canonical example of a monoclonal antibody that has been integrated in to combination chemotherapy for pediatric B-cell non-Hodgkin lymphomas [9,10]. Blinatumomab, a BITE targeting the B-cell acute lymphoblastic leukemia (B-ALL) marker CD19, has shown success in the treatment of B-ALL in adults and has shown to improve survival in pediatric patients with relapsed B-ALL [11–13]. Based on the compelling data in multiply relapsed disease, the Children's Oncology Group (COG) trial is currently investigating blinatumomab for patients with B-ALL in first relapse (NCT02101853) and also recently started investigating it in *de novo* patients (NCT03914625).

A major breakthrough in cancer immunotherapy has been the development of CAR-T cells[6]. A CAR-T cell targeting CD19 (tisagenlecleucel) in relapsed or refractory B-ALL, was the first Food and Drug Administration (FDA) approved gene therapy[6]. In patients with relapsed B-ALL, a single infusion of tisagenlecleucel demonstrated an overall remission rate of 81% at 3 months [14,15].

In addition to antibodies and CAR-T, in recent years there has been increasing interest in immune checkpoint inhibitors. Immune checkpoint inhibitors are a subtype of antibody which seek to 'remove the brakes' on the immune system and restore effector T-cell function by blocking T-cell down regulating pathways such as cytotoxic T lymphocyte-associated protein 4 (CTLA-4), programed death 1 (PD-1) or programmed death ligand 1 (PDL-1) [16]. This class of medications works by potentiating the action of endogenous T-cells, or potentially of CAR-T cells[17].

T-cell malignancies are cancers of T-cell precursors. They can be divided broadly in to T-cell leukemias and peripheral T-cell lymphomas. In children, the most common T-cell malignancy is T-cell acute lymphoblastic leukemia (T-ALL), which represents approximately 15% of pediatric ALL cases[18]. Approximately one third of pediatric non-Hodgkin lymphomas are T-lymphoblastic lymphoma (T-LBL), which shares an immunophenotype with T-ALL[19]. T-ALL is distinguished from T-LBL based on the degree of bone marrow involvement: patients with T-LBL have <25% bone marrow involvement[19]. Pediatric T-ALL is a distinct entity from adult T-cell leukemia (ATL), which is a primarily human T cell leukemia/lymphotropic virus type 1 (HTLV-1) driven cancer[20]. HTLV-1 related leukemias are extremely rare in the pediatric population. By far the most common peripheral T-cell lymphoma in children is anaplastic large cell lymphoma (ALCL). In adults, cutaneous T-cell lymphomas make up a significant portion of T-cell malignancies; these conditions are very rarely seen in the pediatric population.

The successes of immunotherapies in B-cell malignancies have not yet been realized in T-cell malignancies, with few exceptions. We will review some of the challenges of applying immunotherapy to T-cell malignancies and potential solutions. We will discuss potentially clinically relevant immunotherapies, with a focus on T-cell malignancies of relevance to the pediatric population.

2. Challenges of immunotherapy in T-cell malignancies

The advent of immunotherapy has been a major paradigm shift in the treatment of B-cell malignancies, particularly B-ALL. Immunotherapies have not yet been applied as broadly in T-cell related malignancies because of significant challenges presented by the application of immunotherapies to T-cell malignancies. The on-target/off-tumor effects of B-cell immunotherapies have been manageable. For example, the major on-target/off-tumor side effect of CAR-T-19 is the development of persistent endogenous B-cell aplasia [14,15]. The immunosuppressive risk associated with this side effect is abrogated by the supplementation of intravenous immunoglobulin (IVIG).

T-cell directed immunotherapies are likely to have the more general side effects of immunotherapies, including cytokine release syndrome (CRS) and neurotoxicity. However, T-cell directed immunotherapies require special consideration because of T-cell specific possible on-target/off-tumor side effects, including immunosuppression due to T cell aplasia, the concept of fratricide (where any CAR-T directed to kill a T-cell marker would also kill itself, rendering the CAR-T cells inert), and the development of GVHD. We will discuss a general overview of each of these potential challenges (Table 1).

2.1. Immunosuppression

Successful targeting of T-cell malignancies with immunotherapy can be predicted to cause concomitant loss of endogenous T-cells, at least in part. This could lead to profound loss of T-cells, and in children, a clinical scenario analogous to Severe Combined Immune Deficiency (SCID). T-cell directed immunotherapies that cause endogenous T-cell loss may therefore necessitate hematopoietic stem cell transplant (HSCT).

Different strategies have been proposed to address this toxicity without the use of a HSCT. For example, CAR-T cells with so-called suicide genes have been developed[21]. This allows for the transient presence of a CAR-T that could be destroyed after some period of time. Toxicity would be time limited and permanent immunosuppression could potentially be avoided. Another proposed strategy involves using ‘switch’ molecules that bind both the tumor and the CAR-T cells but not endogenous T-cells[22]. CAR-T cells of this design are only active in the presence of the switch molecule and the tumor antigen. This allows for a titratable effect that can be modified by changing the dosage of the switch molecule. When the switch molecule is no longer present, the CAR-T cells are no longer active, and the length of time of collateral T-cell immunosuppression can therefore be minimized. The efficacy of these strategies in human studies have not yet been demonstrated. A final means to avoid this toxicity would be to identify tumor antigens present on malignant T cells, yet absent on normal T cell precursors. Bioinformatic analysis comparing T-ALL blasts to normal T-cells, hematopoietic cells and normal tissues has identified TALLA-1 and hedgehog interacting proteins as potential targets[23]. Currently, there are no immunotherapies targeting either TALLA-1 or hedgehog interacting protein.

2.2. Fratricide

Cell surface markers present on T-lymphoblasts tend to also be present on normal T-cells. Fratricide refers to the concept that any CAR-T cell directed against a T-cell malignancy marker would also target CAR-T cells, potentially destroying its brethren and rendering the CAR-T cells inert. This phenomenon does not occur in CAR-T cells directed against B-cell malignancies because the targets used are not present on the CAR-T-cells.

Furthermore, for CAR-T cells to be clinically successful, they require expansion within the patient[24]. The efficacy of CD-19 directed CAR-T cells has been shown to correlate with the robustness of the expansion within the patient[15,25]. Fratricide could lead to suboptimal or limited expansion within the host, impeding the potential efficacy of the CAR-T. The risk of fratricide appears to be more associated with CAR-T cells that target some antigens as compared with others; however, the biology for this difference is poorly understood. For example, CAR-T targeting CD7 are more prone to fratricide and often require that CD7 is genetically manipulated on the CAR-T itself to avoid fratricide[26]. In contrast, CAR-T targeting CD5 are able to proliferate without manipulation of CD5 on the CAR-T[27]. The data on CD5 and CD7 are primarily in pre-clinical models and the same may not hold true as they are translated in to the clinic.

2.3. Graft versus host disease

GVHD is a multisystem complication of pediatric HSCT characterized by donor T-cells attacking host tissues[28]. The clinical manifestations of GVHD can be severe, and contribute to morbidity and mortality in post-transplant patients[28]. HSCT is not typically part of upfront therapy for childhood T-ALL, however, it is often recommended in children who relapse or have refractory disease[29]. The pathophysiology of GVHD is complex and mediated by T-cell populations[30]. Using immunotherapies to selectively deplete populations of T-cells in patients may put them at increased risk for GVHD if patients subsequently proceed to transplant. T-cell depletion can lead to graft rejection or GVHD, depending on the population depleted. For example, in grafts that have alpha-beta T-cells depleted, there is a decreased risk of GVHD[30]. In contrast, selectively depleting specific populations of T-cells prior to transplant could change the immune balance in the host and lead to subsequent GVHD. For example, regulatory T-cells (Tregs) play an important role in the prevention of GVHD[31]. CCR4 is highly expressed on Tregs[32]. Mogamulizumab, an anti-CCR4 antibody used in adult patients with peripheral T-cell lymphoma, depletes Tregs. Recent studies have shown an increased risk of GVHD in adult patients who received mogamulizumab prior to transplant[33].

2.4. Disease heterogeneity

The ideal immunotherapy targets a marker that is broadly expressed on tumor cells and absent from healthy tissues. A significant challenge in the development of immunotherapies for T-ALL specifically is the inherent heterogeneity of the disease [34,35]. For example, virtually all B-ALL blasts have CD19 present, and this marker is present primarily on B-cells [6]. Common markers present on T-ALL include CD3, CD5 and CD7, all of which are present on T-cells[34]. Targeting any of these markers could lead to significant T-cell aplasia in humans. Furthermore, there are surface antigens that are expressed on malignant T-cell populations in a subset of patients. For example, while CD123 is not commonly expressed in mature or immature T-cell malignancies, it is expressed in some patients with early T-cell precursor T-ALL (ETP T-ALL)[36]. Development of immunotherapies for T-ALL has been hampered by the identification of a marker common across T-ALL blasts and absent from essential healthy tissues.

2.5. Known immunotherapy side effects

The emergence of immunotherapies, particularly CAR-T, have identified serious adverse events specific to this class of therapies. Specifically, cytokine release syndrome (CRS) and neurotoxicity. CRS is a major toxicity associated with immunotherapies, including blinatumomab and CAR-T19 [15,37]. CRS is syndrome similar to hemophagocytic lymphohistiocytosis (HLH) and thought to be caused by massive release of cytokines (including interleukin-6; IL-6) following immunotherapy mediated killing of tumor cells [37–39]. Symptoms include fever, tachycardia, and in severe cases hypotension and respiratory insufficiency[40]. Severity of CRS correlates with disease burden[15]. CRS can be managed with tocilizumab, an IL-6 receptor antibody[41]. The risk of CRS in patients receiving immunotherapies for T-ALL is not yet known, however, given the aggressive

nature of T-ALL in relapse we postulate that patients may be at higher risk of severe CRS, commensurate with their higher disease burden.

Neurotoxicity is an idiosyncratic finding that occurs commonly after CAR-T cell infusion. It includes a range of neurologic symptoms, including most commonly delirium, changes in level of consciousness, headache and speech difficulties[42]. Neurotoxicity is most often reversible but can occasionally be fatal[43]. Severe neurotoxicity is associated with increased systemic cytokines[43]. Similar to CRS, it is difficult to predict the impact of targeting T-cell markers on neurotoxicity.

2.6. Autologous versus allogeneic products

Current clinically available CAR-T products are all autologous products that have been modified to target CD19[6]. Autologous products require that patients have a significantly high absolute lymphocyte count to have cells harvested. Patients with T-cell malignancies may have lower absolute lymphocyte counts, and may be harder to harvest in the relapse setting because of aggressive disease. In this population in particular, allogeneic products may be useful. Allogeneic or ‘off the shelf’ products obviate the need for harvesting the patient’s own cells, and can therefore be used much more quickly in the setting of relapse. However, if an allogeneic CAR-T cell product is used the CAR-T may cause severe GVHD [44,45].

Despite the challenges discussed in the preceding paragraphs, recently great progress has been made toward adopting immunotherapies for T-cell malignancies in children, particularly in T-ALL and ALCL.

3. Immunotherapies for t-all

T-ALL and T-LBL represent approximately 15% of pediatric ALL and lymphoblastic lymphoma. Historically T-ALL had an inferior prognosis to B-ALL; however, with intensification of therapy and adoption of T-cell focused regimens, survival rates are similar to those for B-ALL[46]. Nevertheless, in the setting of relapse, patients with T-ALL have an inferior chance of survival relative to with those with B-ALL, with overall survival rates for patients with relapsed T-ALL of less than 30% [47,48]. This inferior survival is due in large part to a dearth of effective salvage therapies. Thus, novel therapeutics are badly needed for this group of children. A number of different immunotherapies have attempted to target known T-cell antigens (See Table 2). Promising immunotherapy-based strategies are reviewed below.

3.1. Monoclonal antibodies

A potential target for immunotherapy in pediatric T-ALL is the cell surface marker CD38. CD38 is a type II-transmembrane glycoprotein present on the surface of thymocytes, activated T cells and differentiated B cells[49]. CD38 has been shown to be present on pediatric T-ALL blasts at diagnosis and at relapse, demonstrating that the expression of CD38 is not impacted by cytotoxic chemotherapy[50]. Daratumumab is a monoclonal antibody directed against CD38[49]. It has proven activity against multiple myeloma, both as a single agent and in combination with other therapies [51–54]. The safety profile

of daratumumab is favorable when compared to traditional cytotoxic chemotherapy, with reported adverse events including fatigue, anemia, thrombocytopenia and neutropenia. [54,55] The most significant adverse event is an infusion related reaction which can be managed by slowing the rate of infusion and with steroids [54]. This reaction is most likely to occur with the first infusion, and much less likely with subsequent infusions.

Bride and colleagues recently demonstrated pre-clinical efficacy of daratumumab in pediatric T-ALL using a patient derived xenograft model[50]. These results have been replicated by other investigators in mouse models [56,57]. This is the first example of a targeted immunotherapy showing demonstrated efficacy in preclinical models of pediatric T-ALL. Notably, in this study animals with a high burden of disease had a higher risk of death when treated with daratumumab, possibly from overwhelming tumor lysis syndrome. Case series have reported the successful use of daratumumab as salvage therapy in patients with relapsed T-ALL [58,59]. Daratumumab is now being investigated in a clinical trial (NCT03384654) of pediatric T-ALL and B-ALL, combining daratumumab with cytotoxic chemotherapy.

Other monoclonal antibodies targeting CD38 have been developed, such as isatuximab[60]. The safety and efficacy of isatuximab in T-ALL was investigated in a phase I trial (NCT02999633). This trial was terminated prematurely because of an unsatisfactory risk-benefit ratio. This trial used isatuximab as monotherapy. The kinetics of response to anti-CD38 monoclonal antibodies in multiple myeloma was relatively slow, with responses typically seen after a few weeks of treatment. T-ALL is too aggressive of a malignancy to wait for response. Thus, anti-CD38 monoclonal antibodies should be used in combination with cytotoxic agents. Currently, isatuximab is being evaluated in combination with cytotoxic chemotherapy in a phase II study of relapsed ALL and acute myeloid leukemia (AML) in pediatric patients (NCT03860844).

Alemtuzumab (Campath) is a monoclonal antibody directed against CD52. CD52 is a marker present on T-cells, B-cells and NK cells. A small phase II study of single agent alemtuzumab in pediatric patients with relapsed ALL (three of whom had T-ALL) was conducted[61]. Only one patient demonstrated evidence of a response to alemtuzumab and 2/9 evaluable patients had dose limiting toxicities[61]. Results from a phase I trial of alemtuzumab in combination with cytotoxic chemotherapy in adults (CALGB 101,102) were more encouraging[62]. A phase II trial of alemtuzumab in patients with HTLV associated ATL showed a response in approximately half of 29 patients enrolled, however, results were transient with a median progression-free survival time of 2 months[63]. Alemtuzumab has been combined with CHOP, with or without, stem cell transplant in adult patients with peripheral T-cell lymphomas (PTCLS), including ALCL, with a modest response [64,65].

Basiliximab is a monoclonal antibody targeting soluble interleukin-2 receptor alpha (sIL-2Rα, CD25). Basiliximab was originally developed for the prevention of solid organ transplant rejection[66]. CD25 is highly expressed and conserved in T-cell malignancies, including T-ALL[66]. In a pediatric patient with T-ALL, and a severe dermatologic paraneoplastic syndrome (febrile ulceronecrotic Mucha-Habermann disease), basiliximab

was used successfully to induce a remission[67]. The child was subsequently treated with intensive chemotherapy and bone marrow transplantation. This case report is illustrative of a potential role for basiliximab in relapsed or refractory T-ALL.

Recently, novel antibodies targeting anti–IL7 receptor alpha (IL7ra) have been developed [68,69]. IL7ra was shown to be increased in a relapsed patient derived xenograft (PDX) model of T-ALL. Hixon and colleagues showed that anti–IL7ra antibodies demonstrated efficacy *in vitro* and in an *in vivo* model of a single sample of T-ALL[68]. These results are encouraging but require further replication in diverse samples of T-ALL. Akkapeddi and colleagues demonstrated the efficacy of a different anti–IL7ra antibody-drug conjugate that showed effective tumor cell killing in several patient derived xenograft models of T-ALL[69].

3.2. CAR-T

Current clinically available CAR-T cells are autologous T-cells that have been edited to target the marker of interest. At this time, the only FDA approved CAR-T cells target CD-19. As discussed above, targeting T-cell ALL with CAR-T presents challenges not present with targeting B-ALL. Recently, a variety of strategies have been employed to avoid fratricide and T-cell aplasia.

One approach to overcoming the effect of fratricide has been to cause CAR-T cells to omit the target from the CAR-T cell itself. This has been shown to be effective in preclinical models of a CD-7 directed CAR-T [26,70,71]. CD-7 is highly expressed on T-ALL blasts[72]. Gomes-Silva and colleagues demonstrated that a CD-7 directed CAR-T had impaired expansion, presumably secondary to fratricide. They subsequently used CRISPR/CAS9 to disrupt CD-7 expression on the CAR-T targeting CD-7. This led to robust expansion of the CAR-T cells and eradication of T-ALL blasts[70]. They also demonstrated predicted on-target, off-tumor effect of endogenous T-cell depletion, however, CD-7 knockout CAR-T cells retained some capacity to respond to viral peptides. A clinical trial using this CD-7 targeting CD-7 knockout CAR-T in conjunction with costimulatory CD28 is planned (NCT03690011). Cooper and colleagues used a similar strategy to target CD-7 with a fratricide resistant CD-7 knockout CAR-T, achieved using CRISPR genome editing. They also knocked out T-cell receptor alpha chain (TRAC) expression to abrogate the risk of GVHD and allow for the creation of an ‘off-the-shelf’ CAR-T [26]. Png et al. used a protein expression blocker (PEBL) to down regulate CD-7 on CAR-T cells[71]. CD-7 directed CAR-T treated with PEBL were highly successful in killing T-ALL blasts[71].

An ideal way to avoid fratricide and on-target off-tumor effects is to select a target for the CAR-T that is present exclusively or almost exclusively on tumor cells. This has been shown to be possible in an *in vivo* model of ATL. Miyazaki and colleagues designed a CAR-T cell that targeted human telomerase reverse transcriptase (hTERT)[73]. hTERT is a subunit of telomerase, which has been shown to play an important role in tumorigenesis by allowing cells to immortalize[74]. Endogenous cytotoxic T-cells targeting hTERT target adult cancer cells [75,76]. Miyazaki et al. demonstrated that a modified T-cell targeting hTERT led to control of ATL in patient derived xenografts[73]. Pediatric T-ALL cells express hTERT[77]. On-target, off-tumor effects of targeting hTERT in pediatric patients are not known but must

be considered carefully. Similarly, a preclinical study has demonstrated the efficacy of a CD1a-specific CAR T cells for the treatment of cortical T-ALL[78]. CD1a is expressed exclusively on cortical T-cell ALL cells, developing cortical thymocytes and Langerhans cells[78]. CAR-T cells directed against CD1a do not themselves express CD1a and are therefore fratricide resistant[78].

In some models, CAR-T cells independently down regulated the targeted protein on their cell surface. In a CD-5 directed CAR-T model, T-cell subsets downregulated CD-5 when cocultured with a CD-5 directed CAR[27]. Fratricide of CD-5 CAR-T cells was observed initially but was transient. The authors postulate that following the initial fratricide, CD-5 directed CAR-T cells that survived had lower expression of CD-5[27]. This did not impact their efficacy in killing CD-5 positive T-cells[27]. Of note, CD5 is present on approximately 80% of T-ALL blasts[72]. It is also present on most T-cell populations. Inhibition of CD-5 may reduce T-regulatory cells, potentiating auto-immune effects[79]. A phase I clinical trial of a CD-5 CAR-T cell construct is underway and recruiting patients (NCT03081910).

As discussed above, a challenge inherent in developing immunotherapies for T-ALL is the heterogeneity of T-cell leukemias. CD3 is the definitive T-cell marker, and the most specific marker for T-ALL[34]. CD3 has been targeted with an antibody drug conjugate in cutaneous T-cel lymphoma[80]. Colleagues in the United Kingdom have recently developed a CAR-T targeting CD3[81]. CD3 is ubiquitous on normal T-cells, and the CAR-T targeting CD3 caused significant fratricide[81]. The authors used Transcription Activator-Like Effector Nuclease (TALEN) gene-editing to disrupt T-cell receptor expression and thus avoid fratricide[81].

3.3. NK-CAR

Another strategy has been to select non-T-cell effector cells for the CAR, which endogenously do not express the target of interest, typically natural killer (NK) cells. NK-CARs may carry a lower risk of GVHD than CAR-T, may have a lower risk of cytokine release syndrome and have a limited life-span thereby limiting the persistence of on-target off-tumor effects [7,82,83]. Furthermore, NK-CARs can be given off the shelf, obviating the need for collection of patient effector cells and allowing for quicker administration[7]. This is particularly desirous in patients with T-ALL, who often have aggressive disease at relapse which may preclude T-cell collection for autologous CAR-T production.

Despite these potential benefits, NK-CAR production has lagged behind that of CAR-T, because of technical challenges related to genetically engineering NK cells[7]. Furthermore, NK cells require cytokines (specifically IL-2 and IL-15) for expansion[7].

You and colleagues demonstrated the efficacy of CD-7 directed NK cells (dCD7-Car-NK-92MI, mdCD7-CAR-NK-92MI) [82]. These NK-CARs did not express CD-7 and effectively killed CD-7 positive T-ALL blasts *in vitro* and *in vivo*. Of note, some subsets of NK cells do express CD7, particularly those which secrete interferon gamma [84,85]. Similarly, Chen et al. demonstrated an NK derived chimeric antigen receptor cell (NK-CAR) targeting CD-5 had comparable efficacy to a CD5 CAR-T Cell[83]. The same group used

an NK-CAR directed against CD3 with both a CD28 and a 4-1BB costimulatory domain to demonstrate *in vitro* and *in vivo* activity against T-ALL blasts[86].

Monoclonal antibodies and CARs are promising potential therapies for T-ALL. However, the superiority of CAR-T cells or NK-CARs over antibodies has not yet been proven. The optimal CAR-T construct is also not yet clear. Early phase trials of several of these agents are underway. Similar approaches are being studied in peripheral T-cell malignancies. Lessons from the application of these strategies to peripheral T-cell malignancies could potentially be applied to T-ALL.

4. Immunotherapies for Peripheral T-Cell Lymphomas

Peripheral T-cell lymphomas (PTCL) are a diverse and aggressive type of T-cell malignancy. We will focus primarily on anaplastic large cell lymphoma (ALCL), the most common PTCL in childhood[87]. ALCL accounts for approximately 10-15% of Non-Hodgkin's lymphomas (NHL) in children[88]. ALCL can be subdivided in to ALK positive and ALK negative subtypes, with ALK positive tumors making up the majority of pediatric ALCL and having a superior prognosis [88–90]. In patients with relapsed ALCL, ALK inhibitors such as crizotinib, can be used successfully in ALK positive patients[91]. However, limited options exist for patients with relapsed ALK negative ALCL, and those who do not respond to crizotinib. In recent years, several immunotherapies have become available for the treatment of ALCL.

4.1. Monoclonal antibodies and antibody-drug conjugates

Brentuximab vedotin (BV) is an antibody drug conjugate targeting CD30 and carrying the tubulin inhibitor monomethylauristatin E (MMAE)[92]. A landmark phase I trial of BV for adult patients with CD30 positive lymphomas (primarily Hodgkin lymphoma with 2 ALCL patients included) demonstrated a dramatic response with an objective response in 11 out of 17 patients, and a complete response in both patients with ALCL[93]. The ECHELON-2 trial randomized patients with ALCL and other CD30 positive PTCLs to receive either CHP and BV or standard CHOP (cyclophosphamide, doxorubicin, Oncovin, prednisone). Median progression free survival was 48.2 months in the group that received brentuximab and 20.8 months in the placebo arm ($p = 0.0110$). Adverse events were comparable between groups[94].

Based on the successful implementation of BV in to adult regimens, a pediatric phase I/II study was conducted in children with relapsed/refractory Hodgkin's lymphoma or ALCL [95]. Seventeen patients with relapsed or refractory ALCL were enrolled and an overall response rate of 53% was achieved[95]. A COG phase II study (NCT01979536) evaluating BV in combination with conventional chemotherapy for newly diagnosed patients with ALCL recently suspended accrual. A phase I/II trial of BV in combination with the ALK inhibitor ceritinib is currently enrolling patients (NCT02729961).

BV is an antibody-drug conjugate that targets tubulin. Predictably, peripheral neuropathy is a common, and sometimes severe, side effect of BV [94–99]. Five year follow up studies demonstrated resolution or improvement in most patients [96,99]. BV has also been

associated with a risk of progressive multifocal leukoencephalopathy[100], and carries a black-box warning highlighting this risk. Recently, MMAE has also been utilized in an antibody-drug conjugate, AGS67E, directed against CD37[101]. The authors evaluated 17 T-cell lymphoma samples, CD37 was present on approximately 80% of them[101].

Another potential target for T-cell immunotherapy is the cell surface receptor chemokine receptor 4 (CCR4, CD194) [102]. CCR4 is primarily expressed on platelets, T helper type 2 cells, and T regulatory cells, and has been shown to be highly expressed in ATL and cutaneous T-cell lymphoma (CTCL) cells[32]. CCR4 is also expressed in the GI tract and in the brain[103]. CCR4 has been demonstrated to be highly present on pediatric B-ALL blasts[104]. It is not known if it is expressed on pediatric T-ALL blasts. An anti-CCR4 antibody called mogamulizumab has been investigated in ATL and CTCL [105,106]. Mogamulizumab is FDA approved in the United States for treatment of CTCL. In Japan, it is approved for CTCL and ATL. Mogamulizumab has demonstrated efficacy in relapsed and de novo ATL and in CTCL [105,107,108]. Mogamulizumab has also been investigated for the treatment of PTCLs, including ALCL, with disappointing results [109,110]. Despite its presence on platelets, mogamulizumab has not been associated with high rates of thrombocytopenia as a dose limiting toxicity [105,107,108,111]. If CCR4 were targeted with a CAR-T or NK-Cell CAR in the future thrombocytopenia could theoretically be more pronounced.

4.2. Immune checkpoint inhibitors

Immune checkpoint inhibitors are a subtype of monoclonal antibody designed to prevent T-cell exhaustion by targeting immunosuppressive markers such as CTLA-4 and PD-1[112]. Nivolumab is a PD-1 inhibitor that has been used in patients with relapsed and refractory T-cell lymphomas. In a phase 1b trial 13 patients with PTCL were treated with nivolumab with an objective response rate of 40%[113]. Of concern, there has been a report of rapid progression of tumors in three patients with ATL treated with a single dose of nivolumab[114]. Pembrolizumab, another inhibitor of PD-1, was evaluated in a phase II trial which demonstrated on overall response rate of 33% in 13 patients[115]. This trial was halted early because of futility. Ipilimumab, an anti-CTLA-4 antibody, has been studied in conjunction with lenalidomide in patients with NHL who relapsed following bone marrow transplant. This study included a single ALCL patient who was lost to follow up[116]. Although immune checkpoint inhibitors may have a role in the treatment of T-cell related malignancies, the outcomes are unpredictable, and they should be used with caution.

Although modest success has been gained in targeting PTCLs with monoclonal antibodies and immune checkpoint inhibitors, more potent immunotherapies are desired. This has led to the development of CAR-Ts directed at targets of interest for PTCLs.

4.3. CAR-T

Interest in targeting CD30 with CAR-T cells has been present for several decades[117]. The proof of principle of a CD30 directed CAR-T was originally demonstrated in a Hodgkin lymphoma (HL) model[118]. Wang and colleagues subsequently tested a CD30 directed CAR-T with a 4-1BB costimulatory domain in a phase I trial in humans and showed that

CD30 CAR-T was safe, with inconsistent treatment responses[119]. Ramos and colleagues used a CD30 directed CAR with a CD28 costimulatory endodomain to demonstrate the safety and efficacy of a CD30 directed CAR-T in patients with relapsed/refractory Hodgkin and patients with ALCL [120]. As of 2019, six out of nine patients with relapsed Hodgkin's' treated with CD30 directed CAR-T achieved a complete remission[121]. Similarly, 10 out of 19 patients with relapsed Hodgkin's or CD30 positive non-Hodgkin's lymphoma treated with CD30 directed CAR-T had a complete response[122]. Three trials of a CD30 directed CAR-T are recruiting patients (NCT02917083, NCT03383965, NCT04008394). A CAR-T targeting both CD30 and co-expressing CCR4 has shown promising effectiveness in an animal model of HL[118]. A phase I trial of a CAR-T targeting CD30 and co-espressing CCR4 for relapsed and refractory HL and non-Hodgkin lymphoma, including patients with ALCL, is currently undergoing enrollment (NCT03602157).

Maciocia and colleagues have demonstrated preclinical success in using a CAR-T targeting T-cell receptor beta chain constant domains (TRBCS). They showed that normal T-cell populations contain both TRBC1 and TRBC2 cells, whereas malignancies are restricted to either TRBC1 or TRBC2. They subsequently developed an anti-TRBC1 monoclonal antibody and then CAR-T which killed malignant cells but only a subset of normal T-cells, abrogating the risk of immunosuppression [123]. This CAR-T is being evaluated in patients with TRBC1 positive T-cell lymphomas, including ALCL, in an early phase clinical trial (NCT03590574).

A single pre-clinical study has evaluated a CD4 directed CAR-T for PTCL. The CAR-T4 effectively killed CD4 expressing tumor cells *in vitro and in vivo*. CAR-T4 cells that expressed CD4 were eliminated, presumably by fratricide, and non-CD4 expressing T-cells continued to expand[124]. Targeting CD4 with a CAR-T raises the concern of severe T-cell aplasia as an adverse effects in human subjects. This approach may necessitate hematopoietic stem cell transplant. The authors point out that monoclonal antibodies targeting CD4 have been used in human for other conditions, with a favorable safety profile[124]. Particularly in children, the risk of targeting CD4 positive cells is significant. This CAR-T is currently being evaluated in a phase I trial in patients with CD4 positive T-cell leukemias or lymphomas, including PTCL and T-ALL (NCT03829540).

Finally, an anti-CD37 CAR-T has recently been developed, and shown to be active in both B- and T- cell lymphomas[125]. This CAR-T did not appear to be vulnerable to fratricide. Intriguingly, the authors also utilized a bispecific CAR-T that targeted both CD37 and CD19[125]. Bispecific CAR-T targeting dual T-cell specific markers have not yet been developed, to our knowledge.

5. Expert opinion

In the past five years, significant progress has been made toward bringing immunotherapies in to the treatment of children with T-cell hematologic malignancies. However, ongoing challenges remain. The most efficacious target for immunotherapy in T-ALL is not yet known, although in recent years anti-CD38 antibodies such as daratumumab have emerged as having possible benefit and several potential CAR-T cells have been tested and

shown promise in pre-clinical models. Future research should aim to elucidate targets for immunotherapy that are present ubiquitously on T-cell malignancies but absent from normal T-cells and other tissues. In the absence of the optimal target, further study into strategies to limit the life span of CAR-T cells are of great importance to the field. This of course raises the as yet unsolved questions of whether or not CAR-T cell persistence is necessary to maintain a remission and the role of HSCT following CAR-T cell therapy.

As pre-clinically tested constructs move toward clinical trials, we will garner a better understanding of the relative efficacy of different targeted strategies, and the risk-benefit ratio associated with different targets. The on-target/off-tumor adverse events associated with targeting T-cell malignancies are likely to be non-trivial, and difficult to predict from current pre-clinical studies. Expression of a marker on tissue does not necessarily predict side effects. For example, CD38 is expressed on pancreatic islet cells, but studies of daratumumab have not reported increased rates of pancreatitis [51,57,126,127]. Data from phase I trials are required.

An important consideration for the development of targeted cellular therapies for T-cell malignancies is whether to use autologous or allogeneic T-cells. Traditionally, CAR-T cells targeted against CD-19 have used autologous T-cells that are subsequently modified to target the antigen of interest. In T-cell malignancies, it may be particularly advantageous to use allogeneic cells, as the use of healthy donor cells abrogates the need to distinguish allogeneic T-cells from blasts, and avoids the use of T-cells that may be of suboptimal efficacy due to pre-treatment with chemotherapy. However, the use of allogeneic CAR-T comes with a risk of GVHD. The use of CAR-NK cells may have a lower risk of GVHD. Further investigation of the relative efficacy of NK versus T-cell CAR should be explored.

The role of HSCT in the treatment of T-ALL will need to be reexamined if immunotherapies for T-ALL are successfully translated in to clinical practice. HSCT may play a role as consolidative therapy following remission induction with immunotherapy, or as rescue therapy in the case of complete T-cell aplasia due to on-target/off-tumor side effects. Toxicity associated with HSCT, although improved over the past decade, remains significant. As has been demonstrated in adult patients who were treated with mogamulizumab, the risks associated with HSCT and immunotherapy likely vary based on the target of the immunotherapy included, and the relative impact on endogenous T-cells. Strategies that avoid necessitating HSCT may be preferable. What is less clear is the role of HSCT as consolidation following induction of remission with cellular immunotherapies. The role of HSCT as consolidative therapy post treatment with CAR-T 19 is controversial, and practice varies by center[128]. Many of these concerns can only be addressed by a clinical trial. Similarly, optimal supportive care strategies and infection prophylaxis strategies have not yet been elucidated and will need to be studied in tandem with the study of these novel agents.

In pediatric patients, T-cell malignancies tend to be highly aggressive, particularly in relapse. Immunotherapies offer a promising approach to improve outcomes for this group of children. However, based on the kinetics of pediatric disease it is unlikely that certain immunotherapies, such as naked monoclonal antibodies, will be successful as monotherapy.

For example, an early phase trial of single agent isatuximab, an anti-CD38 monoclonal antibody, was closed because of an unfavorable risk benefit ratio (NCT03860844).

Pediatric patients with relapsed T-cell malignancies have a very poor prognosis. Novel strategies for treatment are urgently needed, and the integration of immunotherapies in to the care of these children offers an opportunity for improved outcomes.

6. Conclusion

T-cell malignancies in children are a rare, heterogeneous group of diseases that require intensive treatment. Patients with relapsed disease have few effective options for salvage therapy currently available. Upfront therapies in clinical use today cause significant short- and long-term adverse events. In recent years, promising strategies for immunotherapy including antibodies, antibody drug conjugates and CAR-T cells have been developed and are moving in to clinical trials. Integrating immunotherapies in to future treatment strategies for T-cell malignancies may offer the opportunity for improved survival with less toxicity, and better outcomes for these children.

Funding

DT Teachey is supported by Leukemia Lymphoma Society Translational Research Program grant (MCG 8561-18) and by the NIH/NCI (1R01 CA193776) and a Cookies for Kids Cancer Research Grant

Declaration of Interest

The Children’s Hospital of Philadelphia receives grant support from Novartis. DT Teachey sits on the advisory boards for Amgen, La Roche, Janssen, Sobi, and Humanigen. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

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Article highlights

- Immunotherapies have been successfully applied to B-cell malignancies but have not yet been applied broadly to T-cell malignancies
- In addition to cytokine release syndrome and neurotoxicity, specific challenges exist for targeting T-cell malignancies with immunotherapies that are not necessarily present with B-cell malignancies, including fratricide, profound immunosuppression and graft versus host disease
- Despite these challenges, several CAR-T for T-ALL are under development, including those targeting CD4, CD5 and CD7
- Monoclonal antibodies are also being investigated for use in pediatric T-ALL, particularly those targeting CD38 with open trials of daratumumab and isatuximab
- Monoclonal antibodies and antibody drug conjugates have been integrated in to the treatment of peripheral T-cell malignancies, specifically brentuximab vedotin has demonstrated efficacy in ALCL

Table 1.

Challenges associated with applying immunotherapy to T-cell malignancies.

Immunosuppression	Targeting T-cell malignancies is more likely to lead to profound immunosuppression than targeting other malignancies.
Fratricide	CAR-T cells may also express the antigen they themselves are targeting, leading to the failure of proliferation or death of the CAR-T cells.
Graft versus Host Disease	The risk of multisystem organ disease due to self-directed donor T-cells.
Disease Heterogeneity	Identifying uniform targets in T-ALL is challenging because of the relative paucity of common markers between T-ALL samples.
Immunotherapy Toxicities	Known toxicities due to immunotherapy, such as CRS and neurotoxicity, may be more pronounced in T-cell malignancies because of higher disease burden.
Autologous versus Allogeneic Products	Targeting T-cell malignancies may necessitate the use of allogeneic products which are more readily available for quicker use but carry an increased risk of GVHD.

CAR-T: chimeric antigen receptor T-cell; T-ALL: T-cell Acute Lymphoblastic Leukemia;

Table 2.

Potential targets, targeted therapies and open clinical trials for the treatment of T-cell acute lymphoblastic leukemia (T-ALL) and peripheral T-cell lymphomas (PTCL).

Target	Targeted Therapy	Current Clinical Trials	Eligible Diseases
CD1a	CD1a CAR-T	N/A	Cortical T-ALL
CD3	CD3 NK CAR-T	N/A	T-ALL
CD4	CD4 CAR-T	NCT03829540	CD4 + T-ALL, CD4 + PTCL
CD5	CD5 CAR-T	NCT03081910	CD5 + T-ALL, CD5 + PTCL
CD7	CD7 CAR-T	NCT03690011	T-ALL, CD7+ PTCL
CD25	Basiliximab	N/A	N/A
CD30	Brentuximab CD30 CAR-T	 NCT01979536 NCT02729961 NCT02917083 NCT03383965 NCT04008394	ALCL ALCL CD30+ PTCL ALCL CD30+ PTCL
CD38	Daratumumab Isatuximab	 NCT03384654 NCT03860844	T-ALL T-ALL
CD52	Alemtuzumab	N/A	N/A
CD194	Mogamulizumab CD194/30 CAR-T	N/A NCT03602157	N/A
hTERT	hTERT directed CAR-T	N/A	N/A
IL7 R-a	Antibodies 4A10, 2B8 ADC B12-MMAE	N/A	N/A

CAR-T: chimeric antigen receptor T-cell; NK: natural killer; ADC: antibody-drug conjugate.; T-ALL: T-cell Acute Lymphoblastic Leukemia; PTCL: Peripheral T-cell Lymphoma.