Human Immunology 80 (2019) 400–408

Contents lists available at ScienceDirect

Human Immunology

journal homepage: www.elsevier.com/locate/humimm

Review

Immunotherapy in pediatric B-cell acute lymphoblastic leukemia

Kirk D. Wyatt[a], Richard J. Bram[a,b,*]

[a] Division of Pediatric Hematology/Oncology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States
[b] Department of Immunology, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States

ABSTRACT

Advances in multi-agent chemotherapy and supportive care have dramatically improved survival of children with B-cell acute lymphoblastic leukemia (B-ALL); however, patients with relapsed and refractory disease continue to represent a therapeutic challenge. Hematopoietic stem cell transplant was the first immunotherapeutic approach to be used in the treatment of patients with relapsed or refractory disease. However, novel therapies such as bispecific antibodies that engage T-cells and chimeric antigen receptor T-cells (CAR-T) therapy have emerged as novel FDA-approved options that have the potential to become the new standard of care for these difficult-to-treat leukemias. With multiple immunotherapeutic agents in the drug development pipeline, it is important for cancer researchers and oncologists to be familiar with these agents, including their mechanism of action, side effects and efficacy. In this paper, we review the role of the human immune system in the development and treatment of childhood ALL and provide an overview of current and upcoming immunotherapeutic treatment approaches.

1. Introduction

1.1. Pediatric B-ALL

Pediatric leukemias can be divided into acute vs. chronic and myeloid vs. lymphoid. Acute lymphoid leukemias can be further subdivided into T-cell acute lymphoblastic leukemia (T-ALL) and precursor B-cell ALL (B-ALL). Leukemia is the most common childhood malignancy, accounting for approximately one third of cancers diagnosed in children, and acute lymphoblastic leukemia (ALL) accounts for over three quarters of all childhood leukemias, with the majority of these being of the precursor B-cell type [1,2].

Cancer is the second most common cause of death in children, and leukemia is a leading cause of cancer deaths in this age group [2]. Due in large part to collaborative clinical trials and improvements in supportive care, outcomes in pediatric acute lymphoblastic leukemia have improved dramatically over the past several decades [3]. Ten-year overall survival has increased from 10% or less in the 1960′s to approximately 70% in the 1980′s and over 85% in the present era [3–5].

1.2. Treatment of B-ALL

Since the use of chemotherapy for treatment of pediatric ALL was first reported in 1948, advances arose largely due to introduction of new chemotherapeutic agents or new combinations of active agents to form multi-agent chemotherapy regimens [3,6]. A series of collaborative group trials around the globe have resulted in the treatment approach that is currently considered the standard of care for B-ALL. Though different treatment centers in the United States and around the world may use regimens that vary slightly, the treatment backbone and general approach are the same.

The standard of care for acute lymphoblastic leukemia begins with a 4-week induction regimen, consisting of three or four chemotherapy drugs, with the goal of inducing remission. To prevent relapse, induction is followed by several intensive phases of multiagent chemotherapy over the course of several months, with a focus on central nervous system (CNS) relapse prophylaxis. The final phase of chemotherapy, termed maintenance, consists of daily and weekly myelosuppressive oral chemotherapy, monthly intravenous and oral chemotherapy, and periodic intrathecal chemotherapy. The total duration of therapy is slightly more than two years for females and three years for males [7,8].

Cranial irradiation was historically incorporated into treatment protocols after the risk for CNS relapse was recognized [7]. However, as long-term survival improved due to effective multi-agent chemotherapy regimens, the late effects associated with cranial irradiation, including secondary malignant neoplasms and cognitive deficits, became more apparent and problematic. Subsequently, the use of cranial radiation in B-ALL has largely been abandoned in favor of routine intrathecal chemotherapy for CNS prophylaxis, which has become a cornerstone of ALL treatment [7].

* Corresponding author at: Division of Pediatric Hematology/Oncology, Department of Pediatric and Adolescent Medicine, Mayo Clinic, 200 First St. SW, Rochester, MN 55905, United States.
E-mail address: bramr@mayo.edu (R.J. Bram).

https://doi.org/10.1016/j.humimm.2019.01.011
Received 21 December 2018; Received in revised form 31 January 2019; Accepted 31 January 2019
Available online 01 February 2019
0198-8859/

1.3. Risk stratification for B-ALL: the role of augmenting therapy

Despite the dramatic success with improved outcomes in pediatric patients with B-ALL over recent decades, risk factors in a subset of cases continue to portend a poor prognosis and present a therapeutic challenge to pediatric oncologists. Refinement of risk stratification has led to the practice of augmenting treatment intensity for patients who are at high risk of treatment failure or relapse [9]. The classic risk stratification system, by the National Cancer Institute (NCI), classifies patients as NCI standard risk if their peripheral white blood cell count at diagnosis is less than 50,000/uL at diagnosis and their age is between 1 and 9 years; all other patients are classified as NCI high-risk [10]. Newer risk-stratification systems include a variety of other prognostic factors, including presence of high- or low-risk cytogenetic abnormalities and the early response to induction therapy (including the presence of minimal residual disease [MRD]) [11,12].

The current treatment approach for patients with *de novo* high-risk ALL is to augment the intensity of chemotherapy. Certain high-risk subgroups, such as those with Philadelphia chromosome-positive ALL, may benefit from additional drugs (i.e., tyrosine kinase inhibitors). Some centers also consider hematopoietic stem cell transplantation after induction of remission in certain very high risk subgroups, especially if a suitable matched related donor is available.

Two high-risk patient subgroups which deserve special mention because they continue to represent a treatment challenge include patients with relapsed and refractory disease [4,5,11,13]. Although augmented chemotherapy and stem cell transplant may lead to long-term cure in some of these patients, many patients' treatment courses will be characterized by relapse or progression of disease. Novel therapeutic agents are desperately needed to improve long-term survival in these patient groups, and immunotherapies are emerging as effective treatment strategies in the relapsed and refractory setting.

1.4. Immunotherapy as frontline therapy in pediatric oncology

Whether immunotherapies have a role in up-front treatment of childhood ALL remains to be seen. Although this class of agents has classically been utilized in pediatric oncology as second-line therapies after failure of standard first-line regimens, they are now emerging as frontline therapies in the anti-tumor armamentarium for some cancers. For example, the anti-GD2 antibody dinutuximab (ch14.18) is considered part of the standard of care for MRD eradication in treatment of high-risk neuroblastoma [14]. The incorporation of immunotherapy as frontline therapy for other pediatric malignancies is also the subject of ongoing clinical trials by Children's Oncology Group (COG) and others, including the use of anti-IGF-1R antibody ganitumab in Ewing sarcoma (ClinicalTrials.gov NCT02306161) and brentuximab vedotin (antiCD30/monomethyl auristatin E conjugate) in high-risk Hodgkin lymphoma (ClinicalTrials.gov NCT02166463).

2. Mechanisms for immunotherapeutic approaches

2.1. The role of the immune system in prevention and treatment of malignancy

Before we can understand the ways that immunotherapeutic approaches can be used to treat childhood cancer, we must first understand the human immune system's role in cancer surveillance and the regulation of tumorigenesis.

In the most basic manner, the immune system recognizes tumor cells by the presence of tumor-specific antigens and targets them for destruction [15,16]. Therefore, tumor cells which express "foreign" antigens are targeted for destruction by the human immune system. However, tumor cells evade this mechanism in a number of ways, including downregulating tumor-specific antigens and major histocompatibility complex (MHC) class I molecules, leveraging regulatory T-cells, and upregulating immune checkpoint inhibitors including cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed death receptor 1 (PD-1) on T-cells [16].

Evidence for the role of the immune system in regulating tumorigenesis includes studies on knockout mice with severe combined immunodeficiency (SCID) which revealed that these mice are at higher risk for a variety of tumors [15]. Other mouse strains deficient in innate immune effectors similarly develop a variety of tumors, suggesting that both the innate and adaptive arms of the immune system are vital for preventing tumorigenesis [15]. Furthermore, we know that the role of the immune system in preventing development of malignancy extends to humans, as patients who are on chronic immunosuppression (e.g., solid organ transplant recipients) are at markedly increased risk for developing a wide range of malignancies. This is, perhaps, most commonly recognized as the development of post-transplant lymphoproliferative disorder (PTLD) whereby unchecked lymphoid proliferation occurs on a spectrum that can extend to the development of frank lymphoma [17]. The process is often driven by Epstein Barr virus (EBV). The cornerstone of management is reduction of immunosuppression, which restores the homeostatic checks and balances, leading to regression of the lymphoproliferative process [18]. However, because reduction of immunosuppression increases the risk of transplant allograft rejection, other therapies are often required. While chemotherapeutic agents can be utilized, immunotherapeutic approaches are often used as well. These include rituximab, which is a monoclonal antibody that targets CD20-positive, EBV-infected B-lymphocytes; and cytotoxic T-lymphocytes which target EBV-specific antigens. Thus, even when reduction in immunosuppression is insufficient to prevent PTLD, immunotherapies can be used to control lymphoproliferation.

2.2. Hematopoietic stem cell transplantation

In the 1950's the idea emerged that otherwise lethal doses of myeloablative therapy could be administered for treatment of leukemia and followed by infusion of hematopoietic stem cells from a suitable donor, leading to rescue of hematopoietic function [19]. It soon became clear that transplantation of hematopoietic stem cells also served a second function above and beyond that of simply restoring the body's hematopoietic function after myelotoxic therapy—donor cells could leverage an immunologic response against the host's leukemic cells leading to a graft-versus-leukemia (GVL) effect [20].

The fatal outcomes seen in the earliest attempts to perform HSCT immediately led to the recognition of graft-vs-host disease (GVHD) as a limiting factor. However, Weiden et al. [21] reported that recipients with mild GVHD had a relative relapse rate 2.5 times lower than those without evidence of GVHD, demonstrating the role of immunotherapy (i.e., GVL) as an important component of HSCT success. Additional support for this concept has been provided by the occasional efficacy of withdrawing immunosuppression in relapsed patients after HSCT, and by the increased risk of relapse when donor marrow is T-cell depleted prior to transplant. Finally, the ability of donor leukocyte infusions (DLI) to re-induce remission in patients who relapsed after transplant is further direct evidence for the GVL effect. This has led to the development of hematopoietic stem cell transplantation as a treatment for pediatric B-ALL, and thus was born the age of immunotherapy for B-cell malignancies.

2.3. Antibody-based therapies

Antibody-based therapies involve monoclonal antibodies targeted against tumor-specific antigens. They can come in the form of monoclonal antibodies, antibody-drug conjugates or bispecific antibodies that engage T-cells (i.e., BiTE). The specificity of these therapies allows therapeutic effects to be targeted to tumor cells, with non-tumor cells being relatively spared. The impressive ability of antibodies to

recognize and bind with high affinity and specificity to unique antigens increases the therapeutic index of these reagents by many orders of magnitude in comparison to traditional chemotherapy drugs. However, in some cases, non-transformed cells also express these target antigens and therefore will be killed as innocent bystanders. Another potential disadvantage of the antibody-directed approach, as described previously, is that malignancies may become refractory to treatment by downregulating or mutating targeted antigens, thereby escaping recognition and destruction [16].

2.4. Antibodies targeted to tumor-specific cell surface markers

A number of monoclonal antibodies targeted against tumor-specific cell surface markers are used in clinical practice (e.g., anti-CD20 antibody rituximab [22]; anti-GD2 antibody dinituximab [14]). The mechanism of action for these therapies is fairly straightforward—the antibodies bind to tumor cells, thereby marking them for destruction by the immune system [23]. Use of these therapies in clinical practice is limited by allergic reactions and development of antibodies against the monoclonal antibody product. Their persistence after infusion and ability to stimulate cytotoxic effector cells is also inferior to naturally-occurring antibodies.

2.5. Drug-antibody conjugates

Similar to tumor-specific monoclonal antibodies, drug-antibody conjugates hone in on tumor cells by utilizing the antigen binding domain (Fab) to bind to tumor cells (e.g., anti-CD33/calicheamicin conjugate gemtuzumab ozogamicin [24]; anti-CD30/monomethyl auristatin E conjugate brentuximab vedotin [25]; anti-CD22/calichamicin conjugate inotuzumab ozogamicin [26]). However, rather than stimulating antibody-dependent cytotoxicity, these products primarily work by delivering a payload of a cytotoxic drug once bound to or phagocytosed by cancer cells, thereby leading to targeted cell death [23].

2.6. Bispecific T-cell engagers

Blinatumomab is an example of a bispecific T-cell engager (BiTE). Its structure consists of a protein that fuses within a single polypeptide chain the VL and VH regions from monoclonal antibodies specific for epitopes in the extracellular domains of CD19 and CD3. Upon binding to CD3 on T cells, it bridges them to CD19-positive B-precursor ALL cells, causing TCR-mediated activation and killing of the targeted cells [27].

2.7. Chimeric antigen receptor T-cells (CAR-T)

Chimeric antigen receptors (e.g., axicabtagene ciloleucel [KTE-C19] and tisagenlecleucel [CTL019]) encompass an extracellular single-chain variable fragment (ScFv), which is linked to one or more intracellular signaling domains that activate proliferation and cytotoxicity in T-cells upon MHC-independent recognition of the target antigen [28]. Incorporation of the CD3-zeta ITAM provides “signal 1”, while second and third generation CAR-T constructs include co-stimulatory domains from CD28 and/or 4-1BB to provide the “signal 2” allowing enhanced activation and cytotoxic activity of CAR-T cells. This mechanism allows CAR-T cells to specifically target tumor cells expressing a certain antigen in a manner that is major histocompatibility complex (MHC)-independent, which is important because tumor cells often downregulate MHC class I [29].

2.8. Immune checkpoint inhibitors

T-cell homeostasis is regulated by stimulatory and inhibitory checkpoint mechanisms. Cytotoxic T-lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD1) and its ligand programmed cell death ligand 1 (PD-L1) all act to blunt the T-cell response. Antibodies against these antigens therefore potentiate the action of T-cells and enhance their function of immune surveillance [30].

Immune checkpoint inhibitors have been developed as anti-cancer agents and are currently used in clinical practice outside of the leukemia setting (e.g., anti-PD-1 antibody nivolumab [31]; anti-CTLA4 antibody ipilimumab [32]).

3. Clinical data supporting immunotherapy: efficacy and side effects

3.1. Role of hematopoietic stem cell transplantation

By now, more than one million hematopoietic stem cell transplants (HSCT) in humans have been performed [33], with no sign of slowing in the current rates [34]. HSCT is the accepted standard of care for children with certain high risk leukemias, including those that are relapsed, refractory, or associated with specific high risk features at diagnosis.

Most HSCT in children continue to use supralethal (myeloablative) conditioning regimens, although there has been increased interest in milder treatments (reduced intensity conditioning, “RIC”), especially in older or substantially pre-treated patients with preexisting tissue frailty. Myeloablative conditioning for ALL typically includes several daily fractions of total body radiation, in combination with high doses of intravenous chemotherapeutic agents such as etoposide, cyclophosphamide, or fludarabine. Due to improvements in supportive care, the risks of treatment related mortality due to infection or organ damage, including sinusoidal obstruction syndrome (SOS), have become quite acceptable. Donor stem cells are usually obtained either by harvesting bone marrow or by leukapheresis of peripheral circulating mononuclear cells mobilized from the bone marrow by pretreatment with granulocyte-colony stimulating factor. After stem cell infusion, recipients receive several immunosuppressive drugs, including calcineurin inhibitors and methotrexate, for a limited period of weeks to months to minimize the risk for GVHD until the regenerating immune system has adapted to the new host.

An important issue has been the limited availability of HLA-matched donors. Only about 30% of candidates have a matched sibling, and thus the use of unrelated donors has been dramatically expanded, based on the success of the National Marrow Donor Program (NMDP). Unfortunately, the success of this program has been primarily limited to Caucasian recipients, since HLA haplotypes are conserved in ethnic populations, and relatively fewer non-white donors have registered in the NMDP. A breakthrough in the use of haploidentical donor HSCT came from the observation that shortly following donor stem cell infusion, allo-reactive T cells can be selectively killed by treatment with cyclophosphamide, due to their rapid rates of activation and replication. This spares quiescent hematopoietic stem cells, which divide slowly and which have increased ability to inactivate the drug metabolically [35,36]. Luznik et al. [37] demonstrated the efficacy of post-infusion cyclophosphamide in haploidentical transplantation in a clinical trial that used reduced intensity conditioning, and it has been expanded to include myeloablative conditioning as well. This has broadened the availability of HSCT for children, as often a parent can serve as an effective stem cell donor.

An additional advancement in GVHD prophylaxis has been the use of alemtuzumab, a monoclonal antibody that targets surface CD52, thus causing lysis of normal and malignant T and B lymphocytes, as well as most monocytes, NK cells, and some granulocytes. Given prior to infusion of stem cells, the prolonged half-life of alemtuzumab in the circulation causes an extended period of immunosuppression, and also removes many of the donor T cells *in vivo*, thus substantially reducing the incidence of GVHD [38].

Analysis of outcomes from the Center for International Blood and Marrow Transplant Research (CIBMTR) indicate that with

contemporary conditioning regimens, patients with ALL who achieve first complete remission and undergo unrelated donor stem cell transplant have long-term survival rates of approximately 70% [39]. For patients with relapsed disease in second complete remission, long-term survival rates are approximately 60%, and for patients with advanced disease, long-term survival rates are approximately 40% [39].

4. Antibody-based therapies

4.1. Blinatumomab

Blinatumomab is a BiTE. Below, we will discuss the real-world clinical trial efficacy and safety data, which are summarized in Table 1.

4.2. Indications and FDA-approval

Blinatumomab was initially approved under accelerated approval by the United States Food and Drug Administration (FDA) on December 3, 2014 for Philadelphia chromosome-negative relapsed or refractory B-ALL based on a single-arm study [40]. As required under the accelerated approval program, benefit was confirmed in a randomized trial (TOWER trial, ClinicalTrials.gov NCT02013167), leading to regular approval by the FDA on July 11, 2017. Concurrent with regular approval, labeling was expanded to include patients with relapsed or refractory Philadelphia chromosome positive B-ALL, after the ALCANTARA trial (ClinicalTrials.gov NCT02000427) demonstrated efficacy in patients with Philadelphia chromosome positive B-ALL who demonstrated resistance or intolerance to tyrosine kinase inhibitors. On March 29, 2018, the FDA expanded the indications for blinatumomab to include treatment of pediatric and adult patients with B-ALL in first or second morphologic remission but with MRD of 0.1% or greater based on the BLAST trial (ClinicalTrials.gov NCT01207388) [41].

Pediatric data to support FDA approval of blinatumomab appear to be limited to a phase I/II study, as we could not identify any published phase III data in children. Despite the phase I/II study in children only including three patients (3% of the study population) with Philadelphia chromosome-positive ALL [27], blinatumomab is approved by the FDA for pediatric patients with Philadelphia chromosome-positive ALL [41]. Furthermore, we were unable to identify studies evaluating the efficacy of blinatumomab in pediatric patients who are in morphologic remission with positive MRD; however, FDA approval for this indication extends to pediatric patients. Therefore, approval for some indications appears to be largely based on larger studies in adults, in conjunction with phase II preliminary efficacy and safety data in pediatrics.

4.3. Administration

Because of its short half-life of two hours, blinatumomab is administered as a continuous intravenous infusion [42]. In each 6-week cycle, blinatumomab is given continuously over four weeks, followed by a two-week treatment-free interval. The initial infusion is begun at a dose of 5 μg/m2/d for seven days then escalated to 15 μg/m2/d for the remaining three weeks. Dosing is started at 15 μg/m2/d for the second and subsequent cycles.

In the pediatric phase I/II trial [27], patients were observed in the hospital during the first nine days of treatment (i.e., the first week at the initial dose and the first two days at the higher dose) before transitioning to outpatient administration via continuous infusion pump. Patients with high leukemic burden (i.e., bone marrow blasts > 50%) were administered hydroxyurea or dexamethasone for prevention of cytokine release syndrome (CRS). Intrathecal chemotherapy was administered per local institutional standards. Response was assessed by bone marrow biopsy/aspirate at day 15 of the first cycle and day 28 of each cycle. Patients were treated with at least two—and up to five—6-week cycles of blinatumomab before proceeding to consolidation chemotherapy or hematopoietic stem cell transplant [27].

4.4. Side effects

The most common adverse event at the recommended dose was fever (80%), and it was difficult to clearly attribute many side effects, including as nausea, headache and anemia, to blinatumomab as opposed to the underlying disease. Eight (11%) patients who received the recommended dose developed CRS, with four of these patients developing grade 3 or 4 toxicity. Two of the patients who developed grade 3/4 toxicity permanently discontinued blinatumomab due to the adverse effect [27].

Although blinatumomab has been associated with hypogammaglobulinemia, the effect of this on infection risk, and the role of intravenous immune globulin, remain unclear [43].

4.5. Ongoing studies

Ongoing randomized phase III clinical trials, including one Children's Oncology Group study (i.e., AALL 1331), aim to provide additional efficacy in the relapsed setting (ClinicalTrials.gov NCT02393859, NCT02101853). A phase I study also aims to treat patients with blinatumomab in combination with checkpoint blockade with nivolumab and ipilimumab (ClinicalTrials.gov NCT02879695). The upcoming COG study AALL1731 will be a phase 3 study investigating the role of blinatumomab combined with chemotherapy in patients with standard-risk B-ALL [44], and the St. Jude Total Therapy XVII (ClinicalTrials.gov NCT03117751) incorporates the use of blinatumomab in patients with *de novo* B-ALL.

4.6. Inotuzumab ozogamicin

In August 2017, the FDA approved inotuzumab ozogamicin, an anti-CD22/calicheamicin conjugate, for adults with relapsed or refractory B-ALL on the basis of a phase III trial which demonstrated higher rates of remission when compared to standard chemotherapy. Use in pediatrics patients with relapsed or refractory CD22 + B-ALL is the subject of a phase II study by Children's Oncology Group (AALL1621; ClinicalTrials.gov NCT02981628). Although the study is still underway and preliminary study results have not been publicly released, off-label use despite lack of FDA-approval has been reported in approximately one hundred pediatric patients treated under the FDA's expanded access ("compassionate use") program (ClinicalTrials.gov NCT03127605). A retrospective review of 51 of these patients yields tentative insights regarding side effects and efficacy that require confirmation in a carefully-conducted clinical trial [45].

Sixty seven percent of patients treated with inotuzumab ozogamicin under the expanded access protocol demonstrated complete remission, with 71% of these responders being MRD-negative. As anticipated, CD22 escape was noted in a small subset of patients who underwent CD22 expression analyses post-treatment. Over half of patients who went on to undergo hematopoietic stem cell transplant developed SOS; therefore, morbidity and mortality associated with SOS will need to be closely monitored in current and future studies.

If inotuzumab ozogamicin is proven efficacious in AALL1621, it may gain accelerated approval for pediatric patients with relapsed/refractory disease based on phase II pediatric data combined with phase III adult data, similar to blinatumomab.

The upcoming COG AALL1732 study will be a phase 3 trial incorporating inotuzumab ozogamicin with conventional chemotherapy in patients with newly-diagnosed high-risk B-ALL [44].

4.7. CAR-T cells

One promising and new immunotherapy for pediatric B-ALL is chimeric antigen receptor (CAR) T-cell therapy. Two FDA-approved CAR-T therapies are on the market, namely axicabtagene ciloleucel (KTE-C19) and tisagenlecleucel (CTL019), with the latter being the only

CAR-T therapy approved by the FDA for B-ALL (both are approved for treatment of adults with relapsed or refractory large B-cell lymphoma).

4.8. Manufacture

CAR-T cells are generated from autologous T-cells. Patients first undergo leukapheresis of CD3 + T-cells, which are sent to a clinical laboratory for preparation [46]. The cellular product then undergoes *ex vivo* transduction with a lentiviral vector coding for a chimeric antigen receptor against CD19. T-cells then undergo expansion prior to cryopreservation and are shipped back to the patient's local institution for infusion.

4.9. Administration

Patients usually undergo lymphodepletion within two days to two weeks prior to CAR-T cell infusion to prevent rejection and create space for the cellular product. The most common lymphodepletion regimen includes fludarabine and cyclophosphamide, but a regimen containing cytarabine and etoposide is also acceptable. Lymphodepletion may be omitted in patients with lymphopenia [46].

Patients may receive diphenhydramine and acetaminophen for premedication prior to infusion. Importantly, steroids are not recommended due to the potential to impair the effect of the cellular product. After the product is thawed, it is then infused into the patient. After infusion, patients are expected to develop B-cell aplasia and may receive intravenous immune globulin.

4.10. Axicabtagene ciloleucel

Axicabtagene ciloleucel was approved by the FDA in October 2017 for adults with relapsed or refractory large B-cell lymphoma [47]. An ongoing single-arm phase I/II study (ZUMA-4) is evaluating the safety and efficacy of axicabtagene ciloleucel in pediatric patients with B-ALL that is refractory, relapsed after at least one salvage therapy, or relapsed after hematopoetic stem cell transplant (ClinicalTrials.gov NCT02625480). The study aims to recruit 75 patients. Patients in this study will receive conditioning with fludarabine and cyclophosphamide, followed by $2 \times 10\hat{}6$ CAR-T cells per kilogram. Thus far, data on only four treated patients have been reported in abstract form (Table 1) [48].

4.11. Tisagenlecleucel

Tisagenlecleucel was approved by the FDA in August 2017 for pediatric patients with refractory B-ALL as well as patients with relapsed disease after failure of first-line salvage therapy. Concurrent with approval of tisagenlecleucel, and based on data from CAR-T cell studies, the FDA also approved tocilizumab for patients greater than 1 year of age who are undergoing CAR-T therapy and develop CRS. Due to the risk of CRS, a risk evaluation and mitigation strategy (REMS) was put in place. The REMS requires special certification of prescribers and pharmacists and requires on-site access to at least two doses of tocilizumab which can be administered within two hours of ordering in the event of CRS. In May 2018, the FDA also approved tisagenlecleucel for adults with relapsed/refractory large B-cell lymphoma.

4.12. Phase II efficacy data

The phase II study on tisagenlecleucel probably provides the most comprehensive publicly-available data on the efficacy and side effects of CAR-T therapy in pediatric patients with B-ALL [46]. Clinical efficacy data are summarized in Table 1. Because the study was a single-arm study, comparisons are limited to historical controls. These comparisons, notwithstanding their attendant biases and limitations, appear to favor CAR-T therapy compared to conventional treatments in terms of efficacy.

4.13. Adverse events

Adverse events were common, with nearly all (95%) of patients experiencing therapy-related adverse events. CRS was observed in 77% of patients, with 60% of cases grade 3 or greater. CRS occurred at a median of 3 days post infusion and was noted to happen as late as three weeks post infusion. Nearly half (47%) of patients required intensive care unit admission for management of CRS. Vasopressor support was required in 25% of patients, 13% required intubation and 9% required hemodialysis. Nearly half (48%) of patients who developed CRS received tocilizumab.

Neurotoxicity was another notable adverse effect of tisagenlecleucel, occurring in 40% of patients who received tisagenlecleucel. Most neurologic side effects were temporally associated with CRS, and neurologic effects generally resolved with supportive care.

Patients who enrolled in industry-sponsored/supported trials of tisagenlecleucel are being followed in a 15-year long-term follow up study which will evaluate long-term safety as well as CAR-T cell and lentiviral persistence (ClinicalTrials.gov NCT02445222).

4.14. Cytokine release syndrome

CRS is a recognized, and often serious, side effect of CAR-T cell therapy that deserves special mention. It usually occurs within days of CAR-T cell infusion but has been reported to occur weeks after infusion [46]. CRS is characterized by fever, malaise, capillary leak with hemodynamic instability and multi-organ dysfunction, including neurologic dysfunction [49]. It occurs as a result of cytokine release, including IL-6, by CAR-T cells as they lyse B-cells.

4.15. Grading CRS

More than six systems exist for grading CRS. In an attempt to reconcile discrepant grading systems, the American Society for Blood and Marrow Transplantation (ASBMT) recently developed and published a consensus grading system for CRS [50]. In the consensus guidelines, fever not attributable to any other cause was a requisite symptom, and grading was dependent upon the degree of hypotension and/or hypoxia (Table 2).

4.16. Role of tocilizumab for CRS

Tocilizumab is an anti-IL-6 receptor antibody that interferes with IL-6 signaling. It has been used for treatment of CRS in patients who have received both FDA-approved CAR-T cell products (axicabtagene ciloleucel and tisagenlecleucel) [49]. Retrospective review of off-label use of tocilizumab in 60 patients with a median age of 12 years who underwent CAR-T cell therapy in clinical trials demonstrated a 53–69% response rate, as defined by resolution of CRS within 14 days. Patients received tocilizumab at a median of 3–4 days after onset of CRS, with most patients requiring one to two doses. Despite lack of randomized comparison to a control group and unknown optimal dose and schedule, the FDA approved tocilizumab on the basis of reports of prompt improvement in vital signs after administration, its favorable safety profile and lack of an acceptable alternative. *In vitro* and limited patient data suggest that IL-6 blockade by tocilizumab does not impair CAR-T cell expansion, function or persistence [51–53]. In comparison, corticosteroids impair CAR-T cell expansion and their use should be avoided for CAR-T cell associated CRS [49,51].

4.17. Approaches for preventing CRS

Alternate CAR-T cell dosing strategies, including fractionated (i.e., split) dosing and varying cell doses are being explored as ways to

Table 1
Summary of relevant clinical trial data.

Class	Agent	Reference	Study Phase	Age	N	Subset of B-ALL	CR (%, [95% CI])	Median OS (mo., [95% CI])	Median EFS/RFS (mo., [95% CI])	Comments
BiTE	Blinatumomab	[62]	II	Adult	36	R/R, Ph-negative	42 (26–59)	9.8 (8.5–14.9)	7.6 (4.5–9.5)	
		[63]	II	Adult	189	R/R, Ph-negative	33 (27–41)	6.1 (4.2–7.5)	5.9 (4.8–8.3)	
		TOWER trial [64]	III	Adult	405 (271 blinatumomab)	R/R, Ph-negative	33.6 (28.0–39.5) vs. 15.7 (10.0–23.0) $p < 0.001$	7.7 (5.6–9.6) vs. 4.0 (2.9–5.3) $p = 0.01$	7.3 (5.8–9.9) vs. 4.6 (1.8–19)	– Comparison group received 1 of 4 chemotherapy regimens – Higher SAE rate for blinatumomab compared to chemotherapy (62% vs 45%). – Fourteen percent of patients on blinatumomab developed CRS (24% of these grade 3 or greater)
		ALCANTARA trial [65]	II	Adult	45	R/R, Ph-positive	31 (18–47)	7.1 (5.6-NE)	6.7 (4.4-NE)	
		BLAST trial [66]	II	Adult	21	In CR with positive MRD	80% achieved MRD-negativity		61% at 33 mo.	– Outcome parameters are per row labeling, not per column headers.
		[27]	I/II	Pediatric	49 (phase I) 44 (phase II)	R/R, Ph-positive or negative	39 (27–51)	7.5 (4.0–11.8)	4.4 (2.3–7.6)	– Phase I study determined MTD of 15 ug/m2/d. Outcomes reflect patients treated at MTD. – Three patients (3%) were Ph-positive
CAR-T	Axicabtagene ciloleucel	ZUMA-4 [48]	I/II	Pediatric	Study ongoing	R/R	–	–	–	– Study ongoing. Results of four patients reported in abstract form [48].
	Tisagenlecleucel	[46]	I/II	Pediatric (up to 24 years)	59	R/R	93 at 1 mo. 58 at median 12 mo. follow-up	79% (69–91) at 12 mo	76% (65–89) at 6 mo 55% (42–73) at 12 mo	– Outcome parameters are per row labeling, not per column headers. – Majority of relapses were CD19-negative. – 88% developed CRS, with 31% severe and requiring cardiorespiratory support. – Cytokine levels were predictive of development of severe CRS. – Seventy-one percent of patients in remission demonstrated persistence of tisagenlecleucel and B-cell aplasia as of their last assessment, up to 39 months.
		[46]	II	Pediatric (up to 23 years)	92	R/R	60	19.1	NR 80% (65–89) at 6 mo. 59% (41–73) at 12 mo.	– Seventeen (18%) did not undergo infusion, with 41% of these patients dying prior to infusion, 41% having product-related issues and 18% having adverse events. – Outcome results represent per-protocol analysis on patients who received tisagenlecleucel rather than intent-to-treat – All patients developed B-cell aplasia, which persisted in 83% at 6 months post infusion. – Tisagenlecleucel persisted for a median of 168 days, with a maximum of 617 days.

CI: confidence interval; CR: complete remission; CRS: cytokine release syndrome; EFS: event-free survival; mo.: months; MRD: minimal residual disease; MTD: maximum tolerated dose; NE: not estimable; NR: not reached; OS: overall survival; Ph: Philadelphia chromosome; RFS: relapse-free survival; R/R: relapsed or refractory; SAE: serious adverse event.

Table 2
ASBMT Consensus CRS Grading [50].

CRS Parameter	Grade 1	Grade 2	Grade 3	Grade 4
Fever* with	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C	Temperature ≥ 38 °C
Hypotension	None	Not requiring vasopressors	Requiring a vasopressor with or without vasopressin	Requiring multiple vasopressors (excluding vasopressin)
and/or† Hypoxia	None	Requiring low-flow nasal cannula‡ or blow-by	Requiring high-flow nasal cannula‡, facemask, nonrebreather mask, or Venturi mask	Requiring positive pressure (eg, CPAP, BiPAP, intubation and mechanical ventilation)

Reprinted from Biology of Blood and Marrow Transplantation, in press, Lee DW et al. "ASBMT Consensus Grading for Cytokine Release Syndrome and Neurologic Toxicity Associated with Immune Effector Cells," Page 6, Copyright 2018, with permission from Elsevier.

* Fever is defined as temperature ≥ 38 °C not attributable to any other cause. In patients who have CRS then receive antipyretics or anticytokine therapy such as tocilizumab or steroids, fever is no longer required to grade subsequent CRS severity. In this case, CRS grading is driven by hypotension and/or hypoxia.

† CRS grade is determined by the more severe event: hypotension or hypoxia not attributable to any other cause. For example, a patient with temperature of 39.5 °C, hypotension requiring 1 vasopressor, and hypoxia requiring low-flow nasal cannula is classified as grade 3 CRS.

‡ Low-flow nasal cannula is defined as oxygen delivered at ≤6 L/min. Low-flow also includes blow-by oxygen delivery, sometimes used in pediatrics. High-flow nasal cannula is defined as oxygen delivered at > 6 L/min.

mitigate the risk of CRS without compromising efficacy. Because high tumor burden may predict development of CRS [54], an ongoing pilot study aims to study whether early administration of tocilizumab to patients with high disease burden will decrease the frequency of grade 4 CRS without adversely affecting the efficacy of CAR-T therapy (ClinicalTrials.gov NCT02906371).

4.18. Challenges with CAR-T therapy

One of the major disadvantages of CAR-T therapy is the need for patient-derived cellular product processing. In the phase II study of tisagenlecleucel [46], seven patients did not receive cellular infusion due to "tisagenlecleucel product-related issues" and another seven patients were unable to receive tisagenlecleucel because they died before they could undergo infusion. Improvements in the manufacturing and transport process, including those which expedite product turnaround time, may ameliorate some of these issues.

One potential solution is the generation of universal, "off-the-shelf" CAR-T cells that are not specific to any one patient. This approach relies on gene editing to prevent graft versus host disease by deleting the T-cell receptor on infused lymphocytes [55].

Despite the success of CAR-T therapy, its toxicities cannot be ignored. While the majority of neurotoxic effects appear to be transient [46], only more mature data on late-effects will shed clearer light on these effects. Furthermore, with approximately half of patients requiring intensive care unit support for cytokine release syndrome, strategies to prevent or decrease the severity of CRS are desperately needed.

CAR-T therapy is also expensive and will present a challenge for insurers, patients and health care systems. The list price for tisagenlecleucel is $475,000 for a single infusion [56], a price that does not take into account the costs of supportive care, tocilizumab for patients who develop CRS or other treatments that might be pursued to maintain a durable remission (e.g., hematopoietic stem cell transplant).

One avenue of failure for CAR-T cells is CD19 escape by a CD19-negative B-cell clone. Potential treatments for patients with CD19-negative relapse after CAR-T cell therapy include hematopoietic stem cell transplant or treatment with CAR-T cell products against other B-cell antigens. Promising phase I data of CD22-targeted CAR-T cells suggest that T-cells targeted to alternative antigens may be efficacious; however, as expected, CD22 escape has been observed in patients who relapse after this therapy [57].

4.19. Antibody agents and CAR-T cell therapies under development

As noted above, inotuzumab ozogamicin is the subject of multiple ongoing and planned cooperative group studies in pediatric patients with B-ALL.

Epratuzumab, an anti-CD22 antibody, was evaluated in a Children's Oncology Group Phase I/II study of pediatric patients with relapsed acute lymphoblastic leukemia (ClinicalTrials.gov NCT00098839). Unfortunately, epratuzumab did not result in improved remission rates compared to historical controls who did not receive epratuzumab.

As noted above, axicabtagene ciloleucel CAR-T therapy is the subject of an ongoing pediatric clinical trial (ClinicalTrials.gov NCT02625480) and CAR-T cells targeting antibodies other than CD19 are also under investigation for patients who relapse after CD19 CAR-T therapy [57].

4.20. Mechanisms of treatment failure after immunotherapy

Patients who undergo hematopoietic stem cell transplantation may continue to have persistent disease despite the use of high-dose myeloablative chemotherapy with stem cell rescue and the attendant graft-versus-leukemia effect. Recent studies on the role of minimal residual disease (i.e., persistent levels of tumor cells down to one in 10,000 or 100,000) have demonstrated that patients with even barely detectable leukemic burden at the time of transplant are at greater risk of relapse compared to patients who are MRD-negative [58]. Therefore, it is preferable, though not required, to achieve MRD-negativity prior to undergoing hematopoietic stem cell transplant. This can be achieved with the use of conventional chemotherapy, blinatumomab, or CAR-T cells.

Antibody-based therapies are especially vulnerable to resistance by tumor cells that are negative for the targeted antigen. In the phase I/II study on blinatumomab in children [27], out of fifteen patients who had relapsed and died, four patients had a CD19-negative clone. Additionally, in the phase II study of tisagenlecleucel CAR-T therapy [46], among 27 relapses after CAR-T therapy, 6 had CD-19 unknown status, 1 had CD19 + recurrence and 15 had CD19-negative recurrence (3 of these also with CD19-positive blasts). As discussed above, [57] newer therapies targeting other antigens may play a role in treating these relapses, yet they are susceptible to the same mechanism of drug resistance.

In addition to lack of efficacy, treatment-related toxicity can be another important reason patients die or become unable to complete treatment. In the phase I/II study on blinatumomab in children, 9% (N = 6) patients experienced fatal adverse events; however, three of these patients died after allogeneic stem cell transplant after achieving remission with blinatumomab [27]. When patient deaths after receipt of CAR-T therapy (tisagenlecleucel) were assessed, out of nineteen deaths, 13 occurred due to relapse or progression of disease, two occurred due to infection, two occurred due to complications after other therapies for B-ALL, one occurred due to cerebral hemorrhage in the

context of CRS, and another occurred due to unknown causes [46].

4.21. Future prospects

Notwithstanding the impressive power exemplified by the novel immunotherapeutic approaches described above, it is clear that the major impact on improved outcomes in B-ALL over the last fifty years has resulted from careful administration of generally non-specific antimetabolites and cytotoxic agents. Yet, we may be seeing the limits of intensified chemotherapy, with many studies demonstrating no benefit of further treatment intensification and, worse yet, excessive toxicity [44]. The new successes promised by humoral and cell-mediated immune responses will be welcomed, particularly if long term toxicities from standard chemotherapy and radiation can be avoided.

An additional approach to consider in the future will come from further development and refinement of cell autonomous therapies focused only on genotypically mutant cells. An unusual feature of precursor B-ALL cells is that they often retain their developmentally programmed precarious state of balance between death by neglect and negative selection [59]. Thus, these malignant blasts require ongoing signaling to sustain their proliferation and survival. This underlies the beneficial effect of adding an ABL tyrosine kinase inhibitor to Ph + -ALL therapy, and a current trial using the JAK inhibitor ruxolitinib for ALL cases that carry a cytokine receptor-like factor 2 (CRLF2) activating mutation [60]. Indeed, in a genomics study of 1725 patients with Ph-positive ALL, more than 90% carried activating mutations in kinases typically implicated in cytokine signaling pathways and thus potentially amenable to small molecule inhibition [61]. Conversely, preclinical studies have also demonstrated that the machinery of negative selection remains intact in many of these childhood ALL cases [59]. Enhanced signaling downstream of the B-cell receptor, for instance through inhibition of Shp1 or Ship1 phosphatases, which boosted Syk signaling, can cause activation induced cell death in both normal as well as malignant precursor B-cells. These novel approaches will lead to welcome advances in the future that combine signal transduction directed and immunological therapies with more traditional chemotherapeutics.

5. Conclusion

The use of immunotherapy to treat childhood B-ALL is coming of age and has a bright future. While these therapies are currently only used in the relapsed/refractory setting, their role in targeted upfront therapy is an area of active investigation in the newest generation of cooperative group studies. For example, the upcoming COG study AALL1731 will be a phase 3 study investigating the role of blinatumomab combined with chemotherapy in patients with standard-risk B-ALL, AALL1732 will be a phase 3 study investigating the role of inotuzumab ozogamicin combined with chemotherapy in patients with newly-diagnosed high-risk B-ALL, and AALL1721 will be a phase II study assessing use of tisagenlecleucel following initial blocks of chemotherapy in patients with very high risk B-ALL who achieve first complete remission (ClinicalTrials.gov registrations not yet completed) [44]. Similarly, the St. Jude Total Therapy XVII (ClinicalTrials.gov NCT03117751) study also aims to evaluate the role of blinatumomab and CAR-T therapy in patients with *de novo* B-ALL. We anticipate the movement of these treatments into the frontlines of therapy over the next decade with important implications for other malignancies that will benefit from our experience.

6. Off label usage

This paper describes therapies that are not FDA-approved for treatment of B-ALL. Where appropriate, we have tried to distinguish therapies that have been FDA-approved for certain indications and those that are still under investigation, along with ClinicalTrials.gov identifiers.

Conflicts of interest

The authors have no personal financial conflicts of interest to disclose. Both authors are employed by Mayo Clinic, which is recruiting patients for a clinical trial evaluating axicabtagene ciloleucel CAR-T therapy for relapsed/refractory pediatric B-ALL (ClinicalTrials.gov NCT02625480). The authors' institution is also a participating Children's Oncology Group (COG) institution participating in a phase III study of blinatumomab in first relapse of pediatric B-ALL (ClinicalTrials.gov NCT02101853). The study sponsors had no role in the conception, preparation or decision to submit this manuscript.

References

[1] M.S. Linet, L.A. Ries, M.A. Smith, R.E. Tarone, S.S. Devesa, Cancer surveillance series: recent trends in childhood cancer incidence and mortality in the United States, J. Natl Cancer Inst. 91 (1999) 1051.
[2] R. Siegel, D. Naishadham, A. Jemal, Cancer statistics, 2013, CA Cancer J. Clin. 63 (2013) 11.
[3] J.H. Kersey, Fifty years of studies of the biology and therapy of childhood leukemia, Blood 90 (1997) 4243.
[4] S.P. Hunger, X. Lu, M. Devidas, B.M. Camitta, P.S. Gaynon, N.J. Winick, et al., Improved survival for children and adolescents with acute lymphoblastic leukemia between 1990 and 2005: a report from the children's oncology group, J. Clin. Oncol. 30 (2012) 1663.
[5] H. Ma, H. Sun, X. Sun, Survival improvement by decade of patients aged 0–14 years with acute lymphoblastic leukemia: a SEER analysis, Sci. Rep. 4 (2014) 4227.
[6] S. Farber, L.K. Diamond, Temporary remissions in acute leukemia in children produced by folic acid antagonist, 4-aminopteroyl-glutamic acid, N. Engl. J. Med. 238 (1948) 787.
[7] S.L. Cooper, P.A. Brown, Treatment of pediatric acute lymphoblastic leukemia, Pediatr. Clin. North Am. 62 (2015) 61.
[8] S.P. Hunger, N.J. Winick, H.N. Sather, W.L. Carroll, Therapy of low-risk subsets of childhood acute lymphoblastic leukemia: when do we say enough? Pediatr. Blood Cancer 45 (2005) 876.
[9] E.C. Larsen, M. Devidas, S. Chen, W.L. Salzer, E.A. Raetz, M.L. Loh, et al., Dexamethasone and high-dose methotrexate improve outcome for children and young adults with high-risk b-acute lymphoblastic leukemia: a report from children's oncology group study AALL0232, J. Clin. Oncol. 34 (2016) 2380.
[10] M. Smith, D. Arthur, B. Camitta, A.J. Carroll, W. Crist, P. Gaynon, et al., Uniform approach to risk classification and treatment assignment for children with acute lymphoblastic leukemia, J. Clin. Oncol. 14 (1996) 18.
[11] M.J. Borowitz, B.L. Wood, M. Devidas, M.L. Loh, E.A. Raetz, W.L. Salzer, et al., Prognostic significance of minimal residual disease in high risk B-ALL: a report from Children's Oncology Group study AALL0232, Blood 126 (2015) 964.
[12] I.M. Chen, R.C. Harvey, C.G. Mullighan, J. Gastier-Foster, W. Wharton, H. Kang, et al., Outcome modeling with CRLF2, IKZF1, JAK, and minimal residual disease in pediatric acute lymphoblastic leukemia: a Children's Oncology Group study, Blood 119 (2012) 3512.
[13] E.A. Raetz, T. Bhatla, Where do we stand in the treatment of relapsed acute lymphoblastic leukemia? Hematology Am. Soc. Hematol. Educ. Program 2012 (2012) 129.
[14] A.L. Yu, A.L. Gilman, M.F. Ozkaynak, W.B. London, S.G. Kreissman, H.X. Chen, et al., Anti-GD2 antibody with GM-CSF, interleukin-2, and isotretinoin for neuroblastoma, N. Engl. J. Med. 363 (2010) 1324.
[15] J.B. Swann, M.J. Smyth, Immune surveillance of tumors, J. Clin. Invest. 117 (2007) 1137.
[16] M.F. Wedekind, N.L. Denton, C.Y. Chen, T.P. Cripe, Pediatric cancer immunotherapy: opportunities and challenges, Paediatr. Drugs (2018).
[17] M.R. Petrara, S. Giunco, D. Serraino, R. Dolcetti, A. De Rossi, Post-transplant lymphoproliferative disorders: from epidemiology to pathogenesis-driven treatment, Cancer Lett. 369 (2015) 37.
[18] B. Wistinghausen, T.G. Gross, C. Bollard, Post-transplant lymphoproliferative disease in pediatric solid organ transplant recipients, Pediatr. Hematol. Oncol. 30 (2013) 520.
[19] E.D. Thomas, H.L. Lochte Jr., J.H. Cannon, O.D. Sahler, J.W. Ferrebee, Supralethal whole body irradiation and isologous marrow transplantation in man, J. Clin. Invest 38 (1959) 1709.
[20] D.W. Barnes, M.J. Corp, J.F. Loutit, F.E. Neal, Treatment of murine leukaemia with X rays and homologous bone marrow; preliminary communication, Br. Med. J. 2 (1956) 626.
[21] P.L. Weiden, N. Flournoy, E.D. Thomas, R. Prentice, A. Fefer, C.D. Buckner, et al., Antileukemic effect of graft-versus-host disease in human recipients of allogeneic-marrow grafts, N. Engl. J. Med. 300 (1979) 1068.
[22] V. Minard-Colin, L. Brugieres, A. Reiter, M.S. Cairo, T.G. Gross, W. Woessmann, et al., Non-hodgkin lymphoma in children and adolescents: progress through effective collaboration, current knowledge, and challenges ahead, J. Clin. Oncol. 33 (2015) 2963.
[23] N.A. Buss, S.J. Henderson, M. McFarlane, J.M. Shenton, L. de Haan, Monoclonal

antibody therapeutics: history and future, Curr. Opin. Pharmacol. 12 (2012) 615.
[24] J. Baron, E.S. Wang, Gemtuzumab ozogamicin for the treatment of acute myeloid leukemia, Expert Rev. Clin. Pharmacol. 11 (2018) 549.
[25] R. Kobos, W. Terry, Advances in therapies for non-Hodgkin lymphoma in children, Hematol. Am. Soc. Hematol. Educ. Program 2015 (2015) 522.
[26] M. Rytting, L. Triche, D. Thomas, S. O'Brien, H. Kantarjian, Initial experience with CMC-544 (inotuzumab ozogamicin) in pediatric patients with relapsed B-cell acute lymphoblastic leukemia, Pediatr. Blood Cancer 61 (2014) 369.
[27] A. von Stackelberg, F. Locatelli, G. Zugmaier, R. Handgretinger, T.M. Trippett, C. Rizzari, et al., Phase I/phase II study of blinatumomab in pediatric patients with relapsed/refractory acute lymphoblastic leukemia, J. Clin. Oncol. 34 (2016) 4381.
[28] O. Wilkins, A.M. Keeler, T.R. Flotte, CAR T-cell therapy: progress and prospects, Hum. Gene Ther. Methods 28 (2017) 61.
[29] G. Dotti, S. Gottschalk, B. Savoldo, M.K. Brenner, Design and development of therapies using chimeric antigen receptor-expressing T cells, Immunol. Rev. 257 (2014) 107.
[30] E. Sharon, H. Streicher, P. Goncalves, H.X. Chen, Immune checkpoint inhibitors in clinical trials, Chin J Cancer 33 (2014) 434.
[31] K.L. Davis, A.M. Agarwal, A.R. Verma, Checkpoint inhibition in pediatric hematologic malignancies, Pediatr. Hematol. Oncol. 34 (2017) 379.
[32] M.S. Davids, H.T. Kim, P. Bachireddy, C. Costello, R. Liguori, A. Savell, et al., Ipilimumab for patients with relapse after allogeneic transplantation, N. Engl. J. Med. 375 (2016) 143.
[33] A. Gratwohl, M.C. Pasquini, M. Aljurf, Y. Atsuta, H. Baldomero, L. Foeken, et al., One million haemopoietic stem-cell transplants: a retrospective observational study, Lancet Haematol 2 (2015) e91.
[34] A.K. Singh, J.P. McGuirk, Allogeneic stem cell transplantation: a historical and scientific overview, Cancer Res. 76 (2016) 6445.
[35] M.B. Kastan, E. Schlaffer, J.E. Russo, O.M. Colvin, C.I. Civin, J. Hilton, Direct demonstration of elevated aldehyde dehydrogenase in human hematopoietic progenitor cells, Blood 75 (1990) 1947.
[36] L. Luznik, S. Jalla, L.W. Engstrom, R. Iannone, E.J. Fuchs, Durable engraftment of major histocompatibility complex-incompatible cells after nonmyeloablative conditioning with fludarabine, low-dose total body irradiation, and posttransplantation cyclophosphamide, Blood 98 (2001) 3456.
[37] L. Luznik, P.V. O'Donnell, H.J. Symons, A.R. Chen, M.S. Leffell, M. Zahurak, et al., HLA-haploidentical bone marrow transplantation for hematologic malignancies using nonmyeloablative conditioning and high-dose, posttransplantation cyclophosphamide, Biol. Blood Marrow Transplant 14 (2008) 641.
[38] P.D. Kottaridis, D.W. Milligan, R. Chopra, R.K. Chakraverty, S. Chakrabarti, S. Robinson, et al., In vivo CAMPATH-1H prevents graft-versus-host disease following nonmyeloablative stem cell transplantation, Blood 96 (2000) 2419.
[39] D'Souza A FC. Current Uses and Outcomes of Hematopoietic Cell Transplantation (HCT): CIBMTR Summary Slides, 2017. http://www.cibmtr.org.
[40] FDA. Drug Approval Package: Blincyto (blinatumomab) injection.
[41] FDA. FDA granted accelerated approval to blinatumomab (Blincyto, Amgen Inc.) for the treatment of adult and pediatric patients with B-cell precursor acute lymphoblastic leukemia. https://www.fda.gov/Drugs/InformationOnDrugs/ApprovedDrugs/ucm603171.htm.
[42] M. Klinger, C. Brandl, G. Zugmaier, Y. Hijazi, R.C. Bargou, M.S. Topp, et al., Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab, Blood 119 (2012) 6226.
[43] G. Zugmaier, M.S. Topp, S. Alekar, A. Viardot, H.A. Horst, S. Neumann, et al., Long-term follow-up of serum immunoglobulin levels in blinatumomab-treated patients with minimal residual disease-positive B-precursor acute lymphoblastic leukemia, Blood Cancer J. 4 (2014) 244.
[44] Loh M. Moving the Needle Towards Curing Childhood ALL. https://deainfo.nci.nih.gov/ADVISORY/joint/1218/Loh.pdf (accessed 14 Jan 2019).
[45] D. Bhojwani, R. Sposto, N.N. Shah, V. Rodriguez, C. Yuan, M. Stetler-Stevenson, et al., Inotuzumab ozogamicin in pediatric patients with relapsed/refractory acute lymphoblastic leukemia, Leukemia (2018).
[46] S.L. Maude, T.W. Laetsch, J. Buechner, S. Rives, M. Boyer, H. Bittencourt, et al., Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia, N. Engl. J. Med. 378 (2018) 439.
[47] FDA. FDA approves axicabtagene ciloleucel for large B-cell lymphoma. https://www.fda.gov/drugs/informationondrugs/approveddrugs/ucm581296.htm.
[48] D.W. Lee, A.S. Wayne, V. Huynh, R. Handgretinger, R. Pieters, G. Michele, et al., 1008PDZUMA-4 preliminary results: phase 1 study of KTE-C19 chimeric antigen receptor T cell therapy in pediatric and adolescent patients (pts) with relapsed/refractory acute lymphoblastic leukemia (R/R ALL), Ann. Oncol. 28 (mdx373) (2017) 014.
[49] R.Q. Le, L. Li, W. Yuan, S.S. Shord, L. Nie, B.A. Habtemariam, et al., FDA approval summary: tocilizumab for treatment of chimeric antigen receptor T cell-induced severe or life-threatening cytokine release syndrome, Oncologist (2018).
[50] D.W. Lee, B.D. Santomasso, F.L. Locke, A. Ghobadi, C.J. Turtle, J.N. Brudno, et al., ASBMT consensus grading for cytokine release syndrome and neurological toxicity associated with immune effector cells, Biol. Blood Marrow Transplant (2018).
[51] M.L. Davila, I. Riviere, X. Wang, S. Bartido, J. Park, K. Curran, et al., Efficacy and toxicity management of 19–28z CAR T cell therapy in B cell acute lymphoblastic leukemia, Sci. Transl. Med. 6 (2014) 224ra25.
[52] S.A. Grupp, M. Kalos, D. Barrett, R. Aplenc, D.L. Porter, S.R. Rheingold, et al., Chimeric antigen receptor-modified T cells for acute lymphoid leukemia, N. Engl. J. Med. 368 (2013) 1509.
[53] N. Singh, T.J. Hofmann, Z. Gershenson, B.L. Levine, S.A. Grupp, D.T. Teachey, et al., Monocyte lineage-derived IL-6 does not affect chimeric antigen receptor T-cell function, Cytotherapy 19 (2017) 867.
[54] X.J. Xu, Y.M. Tang, Cytokine release syndrome in cancer immunotherapy with chimeric antigen receptor engineered T cells, Cancer Lett. 343 (2014) 172.
[55] M. Themeli, I. Riviere, M. Sadelain, New cell sources for T cell engineering and adoptive immunotherapy, Cell Stem Cell 16 (2015) 357.
[56] P.B. Bach, S.A. Giralt, L.B. Saltz, FDA approval of tisagenlecleucel: promise and complexities of a $475000 cancer drug, JAMA 318 (2017) 1861.
[57] T.J. Fry, N.N. Shah, R.J. Orentas, M. Stetler-Stevenson, C.M. Yuan, S. Ramakrishna, et al., CD22-targeted CAR T cells induce remission in B-ALL that is naive or resistant to CD19-targeted CAR immunotherapy, Nat. Med. 24 (2018) 20.
[58] P. Bader, H. Kreyenberg, G.H. Henze, C. Eckert, M. Reising, A. Willasch, et al., Prognostic value of minimal residual disease quantification before allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia: the ALL-REZ BFM Study Group, J. Clin. Oncol. 27 (2009) 377.
[59] M. Muschen, Autoimmunity checkpoints as therapeutic targets in B cell malignancies, Nat. Rev. Cancer 18 (2018) 103.
[60] J.D. Roll, G.W. Reuther, CRLF2 and JAK2 in B-progenitor acute lymphoblastic leukemia: a novel association in oncogenesis, Cancer Res. 70 (2010) 7347.
[61] K.G. Roberts, Y. Li, D. Payne-Turner, R.C. Harvey, Y.L. Yang, D. Pei, et al., Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia, N. Engl. J. Med. 371 (2014) 1005.
[62] M.S. Topp, N. Gokbuget, G. Zugmaier, P. Klappers, M. Stelljes, S. Neumann, et al., Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematologic and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia, J. Clin. Oncol. 32 (2014) 4134.
[63] M.S. Topp, N. Gokbuget, A.S. Stein, G. Zugmaier, S. O'Brien, R.C. Bargou, et al., Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study, Lancet Oncol. 16 (2015) 57.
[64] H. Kantarjian, A. Stein, N. Gokbuget, A.K. Fielding, A.C. Schuh, J.M. Ribera, et al., Blinatumomab versus chemotherapy for advanced acute lymphoblastic leukemia, N. Engl. J. Med. 376 (2017) 836.
[65] G. Martinelli, N. Boissel, P. Chevallier, O. Ottmann, N. Gokbuget, M.S. Topp, et al., Complete hematologic and molecular response in adult patients with relapsed/refractory philadelphia chromosome-positive b-precursor acute lymphoblastic leukemia following treatment with blinatumomab: results from a phase II, single-arm, Multicenter Study. J Clin Oncol 35 (2017) 1795.
[66] M.S. Topp, N. Gokbuget, G. Zugmaier, E. Degenhard, M.E. Goebeler, M. Klinger, et al., Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL, Blood 120 (2012) 5185.