BiTEs and CAR-Ts: Immunotherapy in Childhood B-Cell Acute Lymphoblastic Leukemia

by

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ABSTRACT

B-cell acute lymphoblastic leukemia is the most common pediatric cancer, responsible for the most cancer-related deaths in children. Advances in chemotherapy over the past half-century have steadily increased the remission and survival of children with B-cell acute lymphoblastic leukemia to nearly 90%. However, the problems of minimal residual disease and relapsed and refractory disease persist. Personalized, targeted therapies have improved outcomes among the minority of patients for whom chemotherapy is ineffective. Immunotherapy, specifically bispecific T-cell engaging antibody therapy and chimeric antigen receptor T-cell therapy, has proven an effective treatment for relapsed and refractory B-cell acute lymphoblastic leukemia in children. These new modalities, however, have also introduced new adverse side effects to the treatment regimen. Though immunotherapy has increased remission and survival, more work must be done to reduce adverse effects and eliminate relapsed and refractory disease.

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I. Introduction

First described in 1913 in the New York Times as "acute lymphatic leukemia" (Bakalar 2012), acute lymphoblastic leukemia (ALL) is a malignancy of the blood that occurs when lymphoid progenitor cells transform and proliferate, overtaking the bone marrow, blood, and extramedullary sites (Terwilliger and Abdul-Hay 2017). Though its incidence is bimodal, with one peak in children and another peak in adults above age 50, ALL is the most common pediatric cancer, with 80% of ALL occurring in children (“Cancer Statistics Review, 1975-2013 - Previous Version - SEER Cancer Statistics Review” n.d.). Historically a fatal disease, survival rates for childhood ALL have increased dramatically over the past 50 years, from a mere 20% in 1961 to 90% today (Pui and Evans 2013). Despite advances in our understanding of the biology of ALL and resulting improvement of treatment regimens, ALL persists as the most common cause of cancer-related deaths in children (Holmfeldt et al. 2013).

Improvements in ALL treatment over the decades have been consistent and significant. Aminopterin, a folic acid antagonist, was the first treatment to achieve "temporary remissions" in ALL patients in the mid-20th century (Farber and Diamond 1948). Although this initial trial was small and the results were modest, it stands as the pioneering use of chemotherapy to treat childhood ALL (Pui and Evans 2013). In 1962, researchers at St. Jude Children's Research Hospital established what stands to this day as the "backbone" of ALL treatment (Pinkel 1971). Their "total therapy" regimen consisted of three components: remission induction, intensification/consolidation, and continuation/maintenance therapy. Subsequent modifications on this treatment protocol nearly doubled cure rates in the following two decades, with steady improvement in outcome into the 21st century.
With continued advances in our understanding of the biology of ALL, the problem of precisely defining the disease in all its manifestations has become more complex, but the advances in treatment likewise have become more nuanced and personalized to each subtype. Significant as these improvements are, the problem of relapsed and refractory disease remains. Here, we will examine the etiology and current treatment regimens for childhood B-cell ALL as well as recent advances in immunotherapy, specifically bispecific T-cell engaging antibody therapy and chimeric antigen receptor T-cell therapy.

II. Childhood Acute Lymphoblastic Leukemia

a. Etiology & Prognosis

Like most cancers, ALL is a heterogeneous malignancy without a single common causative transforming event. Transformed cells are of the lymphoid lineage, with cells that normally differentiate from lymphoid stem cells to B- and T-lymphoblasts and eventually mature into B- and T-lymphocytes. B-cell ALL manifests as an accumulation of malignant, immature B-cells in the blood, bone marrow, and extramedullary tissue. Though researchers have identified many chromosomal aberrations necessary for transformation (discussed in detail below), a combination of exposures, inherited genetic variation, and chance probably contribute to disease initiation. Studies on exposure to radiation in utero or later weakly correlate with a greater risk for developing ALL, but these studies have not been reproducible (Inaba, Greaves, and Mullighan 2013). Certain genetic syndromes (Down syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, and Nijmegen breakdown syndrome) increase the risk for developing ALL (Terwilliger and Abdul-Hay 2017). Genome-wide association studies
have identified germline allelic variants in four genes that significantly associate with childhood ALL. These genes (*IKZF1*, *ARID5B*, *CEBPE*, and *CDKN2A*) encode regulators of lymphocyte differentiation and proliferation (Papaemmanuil et al. 2009; Sherborne et al. 2010). Despite its heterogeneity, there are common subtypes of B-cell ALL whose genetic lesions have been identified and studied.

Aneuploidy was one of the first cytogenetic aberrations identified in B-cell ALL and serves as a means of risk stratification in patients. Patients with hypodiploid B-cell ALL are known to be a high-risk subgroup, but hypodiploidy itself can be further stratified according to the number of chromosomes. Disease can be classified as near haploid (24-31 chromosomes), low-hypodiploid (32-39 chromosomes), or high-hypodiploid (40-43 chromosomes), though this is a rare subgroup (Pui and Evans 2013). While hypodiploidy describes many thousands of genetic changes, these classifications do not distinguish between "driver" mutations in leukemogenesis and "passenger" mutations that accumulate after transformation (Pui et al. 2011). Genome-wide studies revealed that each class of hypodiploidy has a unique genetic basis for disease. Alterations in receptor tyrosine kinase signaling and Ras signaling characterize near-haploid disease while alterations in *TP53* and *RB1* characterize low-hypodiploid disease (Holmfeldt et al. 2013).

Chromosomal translocations have been most telling about the mechanism of disease initiation, though each alone are not sufficient to generate leukemia (Terwilliger & Abdul-Hay 2017). One famous chromosomal translocation, first reported in 1970, is the Philadelphia chromosome, resulting in the BCR-ABL fusion protein (Propp and Lizzi 1970). Normally a tightly regulated tyrosine protein kinase, ABL becomes constitutively active when fused with BCR. The fusion protein leads to aberrant proliferation and
promotes survival and self-renewal. Another common fusion protein is TEL-AML1. Made of TEL, an ETS family transcription factor required for homing lymphoid cells to the bone marrow, and AML1, the DNA-binding subunit of core-binding factor that recruits transcription factors to activate Hox genes, this fusion protein inhibits transcription, leading to altered self-renewal, proliferation, and differentiation in lymphoid cells (Loh and Rubnitz 2002). Most deadly are diseases carrying an MLL-fusion protein. MLL is a nuclear protein responsible for maintaining expression of certain HOX genes. Fusion with one of its 40 known partners yields a dominant gain-of-function protein that enhances HOX transcription (Ernst, Wang, and Korsmeyer 2002). Over 80% of infants with B-cell ALL harbor an MLL-fusion protein.

Clinically, symptoms of ALL can be nonspecific but result from malignant lymphoid progenitor cells accumulating in the blood, bone marrow, and extramedullary sites (Terwilliger and Abdul-Hay 2017). Signs of bone marrow failure include anemia, thrombocytopenia, and leukopenia. ALL cells in extramedullary sites cause lymphadenopathy, splenomegaly, or hepatomegaly. Their presence in the CNS presents as cranial nerve deficits or meningismus. In addition to these symptoms, patients also experience fever, weight loss, and night sweats (together referred to as 'B symptoms') as well as fatigue, dyspnea, and easy bleeding or bruising. Clinicians diagnose ALL when the patient harbors at least 20% lymphoblasts in the bone marrow or peripheral blood (Alvarnas et al. 2015). Following initial diagnosis, clinicians further characterize the disease using flow cytometry, immunophenotyping, and cytogenetic testing to assess the patient's risk and determine the best method for treatment.

As previously mentioned, the standard of care for B-cell ALL is a chemotherapy regimen first established in the 1960s. Induction of remission,
intensification/consolidation, and continuation/maintenance therapy typically span two to two-and-a-half years. Patient response depends both on biological features of their disease and patient-specific pharmacokinetics (Inaba, Greaves, and Mullighan 2013). Some patients, for example, carry one or two nonfunctional copies of the thiopurine methyltransferase gene. Thiopurine methyltransferase is necessary to metabolize mercaptopurine, a chemotherapeutic agent. Without this metabolism, normal mercaptopurine doses put patients at greater risk for hematopoietic toxicity. Recognizing this pitfall, clinicians began assigning individualized dosing to patients with this genetic variation, to great success (Pui and Evans 2013). Personalized treatment went a step further when the tyrosine kinase inhibitor imatinib (and later, dasatinib) was incorporated into frontline therapy to treat Philadelphia-chromosome-positive B-cell ALL (Schultz et al. 2009). This subtype, once associated with a poor prognosis, now boasts complete remission rates greater than 90%, attesting to the efficacy of personalized treatment.

b. Limitations of Conventional Therapy

Cure rates in children have increased steady over the last half-century, but those whose disease relapses have a prognosis that has not changed at the same pace. Although complete remission rates have approached 90%, the remaining 10% of pediatric patients whose disease is relapsed or is refractory to treatment have not had many options for more effective treatment (Pierro et al. 2017). The approach to treat relapsed and refractory B-cell ALL is unimaginative: reinduction is usually more of the same chemotherapeutic drugs but in a modified schedule or more intense dose (Pierro et al. 2017). The aim of reinduction therapy, however, is not to cure the patient, but to induce remission for long enough to make them eligible for an allogenic hematopoietic
cell transplantation (Luskin and DeAngelo 2017). Unfortunately, even this final line of attack is ineffective, and many patients who receive transplants have poor outcomes.

Relapsed or refractory disease arises from a Darwinian selection driven by the chemotherapeutic agents themselves. Studies comparing the B-cell ALL clones present at diagnosis to those present at relapse have shown that 94% of relapsed clones arose from a clone present at diagnosis and not from a newly initiated disease (Mullighan et al. 2008). Minimal residual disease that survives the initial treatment regimen may carry mutations that confers resistance to chemotherapy. Relapsed clones can be resistant glucocorticoids via mutations in genes involved in glucocorticoid signaling like NR3C1, BTG1, and TBL1XR1 (Klumper et al. 1995). Other mutations—like MSH6 and NT5C2—have been associated with resistance to thiopurines (Pierro et al. 2017). Resistance to these chemotherapeutic agents demonstrates the selective pressure these agents place on disease.

Reinduction therapy is unsuccessful not only because of intrinsic resistance to the chemotherapeutic agents but also because of the toxicity associated with this aggressive treatment. Increasing dose may have modest effects on disease burden, but eventually mortality due to toxicity will supersede the disease as the cause of death (Biondi et al. 2017). Immunotherapy is a promising alternative approach to fighting relapsed and refractory disease.

III. Immunotherapy

With both innate and adaptive arms, the immune system has evolved to both generally and specifically defend against infection. As efficient and complex as the adaptive immune system is, it is not above manipulation. Immunotherapy capitalizes on
the adaptive immune system, either by enhancing the natural cellular response against
cancer cells or by synthetically targeting immune cells to destroy cancer cells. In the
crusade against ALL, the synthetic approach has yielded promising results by
commandeering T lymphocytes in a manner that bypasses their natural limitations
but exploits their natural activity.

a. T-Cell Activation

T lymphocytes, or T-cells, are part of the adaptive immune system, patrolling the
body for foreign antigens and leading multi-cell crusade of eliminating infected cells. T-
cell receptors on the surface of T-cells recognize peptide antigens presented by the
major histocompatibility complex (MHC) protein at the surface of somatic cells. All
nucleated cells express MHC class I, which presents endogenous antigens at the
cell surface. CD8+ T-cells, known as cytotoxic T-cells, recognize MHC class I and their
associated antigens. Only professional antigen-presenting cells express MHC class II,
which presents exogenous antigens, indicating infection. CD4+ T-cells, known as helper
or regulatory T-cells, recognize MHC class II and their associated antigens. MHC
recognition by the T-cell receptor, however, is not sufficient to activate a T-cell. Naïve T-
cells require a co-stimulatory molecule (CD28) to also engage with the antigen-
presenting cell. Without this second signal, T-cells are susceptible to anergy, or
desensitization to the antigen. Engagement of the MHC with the T-cell receptor and the
co-stimulatory molecule creates an immune synapse. The T-cell receptor and the co-
stimulatory molecule come into close proximity to one another, initiating a cascade of
intracellular signaling that leads to T-cell activation (Owen et al. 2009).

Once activated, T-cells undergo clonal expansion and differentiation, ultimately
maturing into their full effector functions. Immediately after activation, both CD4+ and
CD8+ T-cells secrete cytokines that aid in the subsequent immune response and in T-cell maturation. Cytokines released by CD4+ helper T-cells stimulate clonal expansion of the T-cell and recruit and activate other immune cells to kill target cells. Cytokines released by CD8+ cytotoxic T-cells stimulate clonal T-cell expansion, and target cell killing, as well as the recruitment and activation of other immune cells to kill target cells. Thus, T-cells defend the body in two ways: by regulating effector response from other immune cells and by directly attacking target cells (Owen et al. 2009).

b. BiTEs

A bispecific T-cell engaging antibody (BiTE) engages T-cells to destroy ALL cells by physically juxtaposing T-cells and ALL cells and activating the T-cells. Made up of the variable antigen-binding domains of two antibodies linked by a peptide, BiTEs capitalize on the high affinity and avidity of antibodies to their antigens (Ribera et al. 2015). Blinatumomab, a BiTE from Amgen Inc currently used to treat relapsed or refractory ALL, binds T-cells with an anti-CD3 arm and ALL cells with its anti-CD19 arm. CD19 is expressed by all B cells. Unlike with the natural T-cell response described above, CD19 does not need to be presented by the MHC for the T-cell to be activated. By forcing the ALL cells and T-cells into such close proximity, Blinatumomab leads to the formation of an immune synapse and hence the destruction of the ALL cell (Aldoss et al. 2017).

In practice, Blinatumomab is an effective therapeutic modality both because of its function and because of its structure. Because its function is based on highly specific antibody-antigen binding, Blinatumomab is clinically efficacious at picomolar concentrations (Nagorsen et al. 2012). In addition, because its mechanism of action relies on T-cell activation, Blinatumomab’s effects are increased by signal amplification from the T-cell receptor (Aldoss et al 2017). Not only is it mechanistically potent, but its
structure makes it especially practical in the clinic. Because Blinatumomab is made up of two variable antigen-binding regions and a peptide linker, it is about one-third the size of an antibody (Nagorsen et al. 2012). Its minuscule size means that Blinatumomab has a short serum half-life. Though its rapid clearance means it must be administered by continuous intravenous infusion, it also gives clinicians the flexibility to halt treatment should the side effects be particularly dangerous.

Administration of Blinatumomab yields results that logically flow from the T-cell activation theory. Although levels of circulating B- and T-cell drop immediately after initial infusion (Zhu et al. 2017), effector T-cell levels exceed normal levels within a few days. Levels of both CD4+ and CD8+ effector T-cells increase, but levels of naïve T-cells remain stagnant. This is not surprising since Blinatumomab is facilitating the activation and subsequent clonal expansion and differentiation of T-cells. Also not surprising is the hypogammaglobulinemia that follows treatment. Blinatumomab targets T-cells toward any CD19-expressing cells, which are not only B-cell ALL but also normal B lymphocytes and plasma precursors. Though expected, this effect puts patients at greater risk for infection because although naïve B cells recover from this depletion, mature B cells and plasma cells do not (Zugmaier et al. 2014).

Blinatumomab is effective at treating relapsed and refractory B-cell ALL in children, as demonstrated by clinical trials. In one trial, 39% of patients achieved complete remission and 52% of those patients tested negatively for minimal residual disease (von Stackelberg et al. 2016). However, the efficacy of Blinatumomab comes at a cost. Two major adverse effect of Blinatumomab treatment are cytokine release syndrome and neurotoxicity (Aldoss et al. 2017). Patients with high leukemic burden at initiation of treatment were more likely to experience cytokine release syndrome, but pretreatment
with dexamethasone proved an effective prophylaxis (Topp et al. 2014). Neurotoxicity presented in adult patients more frequently than in children and could likewise be mitigated using dexamethasone. Thus although side effects of Blintumomab are not mild, they are manageable.

c. CAR T-Cell Therapy

Like BiTEs, chimeric antigen receptor (CAR) T-cells use antibody affinity to \text{CD}19 to juxtapose T-cells and B-cell ALL cells. The T-cells involved in this interaction, unlike with BiTEs, are themselves genetically modified to exclusively target \text{CD}19. Rather than rely on the T-cell receptor recognizing an antigen presented by MHC, CARs replace the extracellular domain of the T-cell receptor with the single-chain variable fragment of a monoclonal antibody targeting \text{CD}19. The transmembrane and intracellular portions of the T-cell receptor are unaltered, but CAR T-cells also express a co-stimulatory domain, either 4-1BB or CD28. Though the extracellular single-chain variable fragment is sufficient to bring the T-cell and target cell into close proximity, the co-stimulatory domain is necessary for T-cell activation, expansion, and persistence (Savoldo et al. 2011; Campana, Schwarz, and Imai 2014). These T-cells are isolated from the patient by leukapheresis, transduced with the CAR vector, expanded, then re-infused into the patient a few weeks later (Aldoss et al. 2017).

Complete remission rates in pediatric patients with refractory and relapsed B-cell ALL treated with CAR T-cell therapy far exceed those achieved by Blintumomab. The most successful trial to date was a collaboration between the University of Pennsylvania, Children’s Hospital of Philadelphia, and Novartis using their recently FDA-approved CTL019 CAR T-cell therapy (Grupp et al. 2015). This trial was conducted on 30 high-risk patients, 25 of whom were children. Only 3 of the patients enrolled in this trial had
primary refractory disease: 18 patients had relapsed after allogenic hematopoietic stem cell transplantation and three patients were refractory to blinatumomab. Despite these seemingly impossible hurdles, CTL019 achieved complete remission in 90% of the patients. Even more impressive, 15 of the patients who went into complete remission did not receive further therapy (Maude et al. 2014).

As remarkable as the final results were, the patients experienced serious toxicities during treatment. Just as with Blintumomab, the main adverse effects of CAR T-cell therapy are cytokine release syndrome and neurotoxicity. Most patients experienced mild symptoms of cytokine release syndrome within the first 2 weeks of treatment. These symptoms were successfully mitigated using fluids and antipyretics (Luskin and DeAngelo 2017). Some patients, however, experienced more severe symptoms including high fever, respiratory distress, and organ failure (Maude et al. 2014). Neurotoxicity, manifesting as confusion, is another result of cytokine release syndrome. Though neurotoxicity is usually manageable, one CAR T trial by Juno Therapeutics reported a fatal cerebral edema and herniation (Keshavan and Garde 2016). The question of why Juno Therapeutics’ CAR T therapy yielded such an extreme adverse event where as Novartis’ CAR T therapy did not remains unanswered.

d. Limitations of Immunotherapy

Despite its unique approach to treating patients with relapsed and refractory B-cell ALL, immunotherapy in its current state is not the saving grace for all patients. Both Blinatumomab and CAR T-cell therapy yield better outcomes for patients who at the start of treatment had lower leukemia burden (Aldoss et al. 2017). Even when the therapy is effective for patients with particularly aggressive disease, relapse following immunotherapy can present as a new disease. The specificity of Blinatumomab and CAR
T-cell therapy is a double-edged sword, simultaneously allowing for a strong targeted attack but limiting the effort to attacking only CD19+ cells. B-cell ALL’s heterogeneity and propensity to mutate persist as challenges to therapy.

In the case of Blinatumomab, relapse has been linked both to limitations of its own activity as well as to a changing disease profile. B-cell ALL presents in the bone marrow, blood, and extramedullary sites, and while Blinatumomab is effective at eliminating disease in the blood and bone marrow, it has been observed to have less activity in extramedullary sites (Topp et al. 2014). Consequently, in patients who relapse following Blinatumomab treatment, extramedullary relapse is over-represented. Even when Blinatumomab is effective in all sites of disease burden, the disease itself may become resistant to the treatment. In 10-15% of relapse cases following Blinatumomab, relapsed disease was CD19-negative (Topp et al. 2012). One study described a patient who received Blinatumomab treatment twice, relapsing after both instances. Following the second relapse after Blinatumomab, her disease had lost nearly all B-cell markers including CD19, manifesting instead with a myeloid phenotype (Zoghbi et al. 2017). As was the case with chemotherapy resistance, the selective pressure of Blinatumomab resulted in a disease totally resistant to the treatment.

CAR T-cell therapy shares some limitations with Blinatumomab and has its own unique drawbacks. Just like Blinatumomab, CAR T-cell therapy exclusively targets CD19-expressing cells, making the treatment ineffective against CD19− ALL. Investigators at the National Cancer Institute are tackling this hurdle head-on by developing CAR T-cells bearing anti-CD22 single-chain variable fragment. CD22, another B-cell-specific antigen, has proven to be an effective means of targeting CD19− ALL.
ALL. In a trial with relapsed pediatric patients, the majority of whom had relapsed following anti-CD19 CAR T-cell therapy and harbored CD19- disease, anti-CD22 CAR T-cell therapy resulted in minimal residual disease-negative complete remission in 8 out of 10 participants (Shah et al. 2016). The CAR T modality thus lends itself to modification depending on the patient's needs. However, this property can also be limiting: because CAR T-cells must be produced anew for each patient, treatment for this rapidly progressing and rapidly mutating disease is not immediate. In addition to keeping patients stable as they await their CAR T-cell infusion, hospitals also bear the burden of the intensive care required when patients inevitably experience the adverse effects associated with CAR T-cell therapy. Though these drawbacks make CAR T-cell therapy an expensive and risky treatment option, the results speak for themselves.

**IV. Conclusion**

Childhood B-cell acute lymphoblastic leukemia has been steadily approaching a cure over the past half century of biological research and treatment advancements. Though frontline therapy has persisted as the cause of remission for most patients, the small fraction of pediatric patients with relapsed or refractory disease have a growing number of treatment options that target their unique malignancy. Advancements in immunotherapy through the development of bispecific T-cell engaging antibodies and chimeric antigen receptor T cell therapy have extended the lifespans of patients who less than a decade ago would have had a dire prognosis. As researchers continue to refine their understanding of the biology of this complex disease and concurrently refine their
treatment strategies, patients can look forward not only to longer survival, but to less toxicity during therapy.

Remission and survival rates of patients treated with BiTEs or CAR T-cell therapy are promising, but there is much room for improvement in both of these modalities. Currently, both Blinatumomab and anti-CD19 CAR T-cell therapy are approved for use only in patients with relapsed or refractory disease. However, both of these modalities function through mechanisms distinct from frontline chemotherapy and could therefore potentially work synergistically with frontline therapy if administered early on. There is an ongoing phase II clinical trial (NCT02143414) assessing the efficacy of chemotherapy, Blinatumomab, and dasatinib combination therapy in geriatric patients with B-cell ALL. The drawback of administering immunotherapy early on is the potentially unnecessary risk of severe toxicity (cytokine release syndrome, neurotoxicity) associated with these modalities in addition to the toxicity patients experience with chemotherapy alone. While it is preemptive to suggest that immunotherapy be administered as frontline therapy for all patients, further refinement of patient risk stratification can help clinicians predict the progression of disease and appropriately weigh the risk of adverse events with the potential for remission without relapse. For example, one issue with CAR T-cell therapy is the length of time patients must wait for their cells to be ready for infusion. Perhaps more accurate risk stratification could eventually lead clinicians to preemptively collect and engineer T cells from a patient likely to relapse following frontline therapy. This future may not be far off given the pace of advancement and motivation to finally cure ALL.
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