Have CD19-directed immunotherapy and haploidentical hematopoietic cell transplantation transformed pediatric B-cell acute lymphoblastic leukemia into a chronic disease?

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ABSTRACT

The treatment of pediatric B-cell acute lymphoblastic leukemia (B-ALL) has undergone several recent advancements, leading to an increased amount of treatment options for relapsed patients. The development of immunotherapies such as anti-CD19 chimeric antigen receptor (CAR) T cells and bispecific T-cell engagers has given clinicians therapeutic options with less expected toxicity when compared to standard re-induction chemotherapy. This is especially beneficial in patients with toxicities from their prior treatment. Along with this, the emergence of haploidentical hematopoietic cell transplantation (HCT) has increased opportunity for patients to receive HCT who may not have had an available matched donor. We present four patients who have received all of these therapies in different combinations to treat multiple relapses. Because of the success of achieving remission as well as decreasing toxicity, the patients are alive and well up to 15 y after the original B-ALL diagnosis, rendering this as a chronic disease for them.

Introduction

In the last 10 y, there have been significant advances in the treatment of B-cell precursor acute lymphoblastic leukemia (B-ALL). Blinatumomab, a bispecific T cell engager (BITE), engages CD3+ T cells directly to CD19+ targeted B-ALL cells. Blinatumomab was FDA approved for the treatment of B-ALL in December 2014 and has become an important component of cooperative group protocols and is widely used following relapse to successfully induce remission. In addition, anti-CD19 chimeric antigen receptor (CAR) T cells, FDA approved in July 2017, are commonly applied for relapsed B-ALL. They have been used effectively either as definitive treatment or as a bridge to allogeneic hematopoietic cell transplantation (allo-HCT). To date, these immunotherapies have been associated with decreased toxicity, diminished neutropenia and opportunistic infections, improving the patient’s performance status and therefore patient’s ability to receive further therapy when needed. Imatinib is a selective BCR-ABL tyrosine kinase inhibitor (TKI), while dasatinib is a dual BCR-ABL and Src family TKI. These agents have drastically improved the outcomes for patients with Philadelphia chromosome positive (Ph+ ALL) who previously were unlikely to be cured with chemotherapy alone.

Donor choice for allo-HCT has evolved as well. Matched related and unrelated allo-HCTs have been the standard of care for high-risk and relapsed B-ALL for half a century. However, in the last decade haploidentical HCT (haplo-HCT) with post-transplant cyclophosphamide (PT-CY) has proven to be a practical and reliable alternative approach. It is easily applicable by many transplant centers and readily available for most patients. Along with emerging therapeutic options, improved supportive care has led to reduced morbidities in patients. Herein, we present four patients who have benefited from these promising treatment modalities leading to repeated inductions of complete remissions (CR) and prolonged disease-free survival. Our cases illustrate that these therapeutic advances, in addition to improved supportive care, have altered the landscape of pediatric B-ALL transforming it into a chronic disease.

While the definition of chronic disease varies across the literature and between medical organizations, common criteria typically include a prolonged, often perpetual, course of illness requiring ongoing medical attention and an associated functional impairment. In order to unify the definition and appropriately allocate resources within healthcare, it has been suggested to utilize the Merriam Webster definition of chronic, which is something that is “continuing and occurring again and again for a long time”. This definition specifies the need for ongoing monitoring and treatments with the goal of continued survival.

Case series

Case 1: BITE, UCBT, CAR-T, BITE, haplo-BMT

Patient #1 was diagnosed with B-ALL at 1.6 y of age and developed an early isolated central nervous system relapse. He was treated according to the COG AALL 1331 protocol receiving induction followed by blinatumomab 15 μg/m²/
24 hr for two cycles. He then proceeded to a four of six antigen-matched unrelated cord blood transplant (UCBT) in second complete remission (CR2) following conditioning with Busulfan Fludarabine and Melphalan. Unfortunately, he relapsed 2.5 months later. The patient was then enrolled into an anti-CD19 CAR-T cell trial (University of Washington) requiring three separate infusions which resulted in brief responses due to short-lived persistence of the infused T cells. He then was treated on a second CAR-T cell clinical trial (Children’s Hospital of Philadelphia) but failed to respond for the same reason. In addition to lack of persistence or exhaustion of CAR-T cells, failure to respond may be due to development of escape variants with loss of CD19 on B-ALL cells. After returning to our institution, he received reinduction chemotherapy for two weeks, and since his leukemia blasts remained CD19-positive, this was followed by a cycle of blinatumomab 15 μg/m²/24 hr, achieving again a minimal residual disease (MRD) negative remission. He quickly proceeded to a second transplant while in CR4 using his mother as the bone marrow donor. He received myeloablative conditioning comprising fractionated total body irradiation (f-TBI 200 cGy x 6) followed by fludarabine (FLU) 30 mg/m² for four doses. PT-CY (50 mg/kg/dose) was infused on days +3 and +4 following a T-replete haplo-bone marrow transplant (BMT). He remains alive and disease-free for 4.9 y post-transplant (7.8 y since ALL diagnosis, Figure 1). This case underscores the utility of blinatumomab in treating relapsed refractory ALL even after failing anti-CD19 CAR-T cell therapy. It also highlights the advantage of having a readily available haploidentical donor to promptly move to HCT when a matched sibling donor is not available.

**Case 2: MMUD-BMT, BITE, haplo-BMT, CAR-T, haplo-CD34 +**

Patient # 2 was diagnosed in Mexico at age 13 y with B-ALL and presented to us during her third relapse at age of 20 y. After achieving a CR4 with four cycles of Hyper-CVAD (CY, vincristine, doxorubicin, dexamethasone) she was conditioned with CY, f-TBI (1200 cGy) and anti-thymocyte globulin and underwent a one antigen mismatched unrelated donor (MMUD)-BMT. She had a bone marrow relapse 2.8 y later and was reinduced with a two-week course of chemotherapy followed by blinatumomab 15 μg/m²/24 hr for 2 cycles, achieving an MRD negative CR5. She then underwent a T-replete haplo-BMT from her brother after conditioning with busulfan (BU), FLU and melphalan (MEL) followed by PT-CY. She again had a bone marrow relapse 1.2 y post-BMT. T cells were collected just prior to her 26th birthday and she received CAR-T cells (Tisagenlecleucel) following lymphodepleting chemotherapy. She then developed prolonged pancytopenia with an aplastic bone marrow requiring prolonged granulocyte colony-stimulating factor support and remained red cell and platelet dependent for over six months. As she continued to have full donor chimerism, she was rescued with CD34 + selected cells from a peripheral blood stem cell (PBSC) collection from her haploidentical donor (brother). At age 27.8 and remarkably 15 y since her original diagnosis she remains in remission with trilineage engraftment and normal counts but continues to have B cell aplasia.

**Case 3: BITE, MSD-HCT, CAR-T, haplo-BMT**

Patient # 3 presented with B-ALL when she was 2.3 y old and relapsed 13 months later. She was reinduced according to ALL-R3 protocol (dexamethasone, mitoxantrone, vincristine, peg-asparaginase) but failed to achieve remission having 24% bone marrow blasts at the end of re-induction chemotherapy. She was then treated with blinatumomab (15 μg/m²/24 hr) leading to an MRD negative CR2 after the initial cycle but with a detectable MRD of 0.04% after the second cycle. While off blinatumomab for two weeks her bone marrow blasts increased to 2.2% the day she began her HCT preparative regimen. She
underwent a matched sibling (MSD) PBSC transplant following CY, t-BMT (1200 cGy) conditioning but not unexpectedly relapsed six months later. She was subsequently treated with CAR-T cells (Tisagenlecleucel). She continued to have B cell aplasia for 12 months and found to have a CD19+ bone marrow relapse just two months after recovery of her B cells. She once again received induction chemotherapy and achieved an MRD negative CR4. She then underwent a T-replete haplo-BMT from her mother following BU-FLU-MEL conditioning. She is now 7 y old and remains in remission at 1.1-y post haplo-BMT and 4.9 y since her original diagnosis. While this patient was clearly sensitive to both anti-CD19 immunotherapies, blinatumomab and CAR-T cells, she appeared to relapse as soon as exposure to these agents was waning. Her first transplant became possible following a remission achieved with blinatumomab, and CAR-T cell treatment allowed a prolonged interval between her first and second transplants (2.2 y) which we and others have shown to be associated with improved outcomes.11,12

Case 4: BITE, haplo-BMT, haplo-HCT
Patient # 4 was diagnosed with Ph+ B-ALL when he was 8.8 y old and was treated on COG protocol AALL0622 completing therapy after 2.5 y. He remained in remission for more than 7 y when he was found to have a bone marrow and central nervous system relapse after presenting with a facial palsy. Reinduction chemotherapy according to COG AALL1331 with addition of dasatinib induced an MRD-remission but was complicated by disseminated candidiasis. Due to his overwhelming fungemia, further myelosuppressive chemotherapy was prohibited and after a prolonged delay in therapy it was decided to treat him with blinatumomab and daily dasatinib. He received a total of five 28-day cycles of blinatumomab until his candidiasis had been adequately treated. He then proceeded to a T-replete haplo-BMT from his mother following BU-FLU-MEL conditioning. Unfortunately, he failed to engraft and was salvaged with a second haplo-HCT after receiving a single-day multiagent immunosuppressive conditioning with 200 cGy TBI followed by CY, FLU and alemtuzumab all given on day –1 with unmanipulated G-CSF mobilized PBSC from the same donor infused the following day.13 The proximal timing of alemtuzumab in this regimen allows for in vivo depletion of donor T cells without the need for graft manipulation or PT-CY. The patient engrafted promptly and remains alive and disease-free more for than 3 y from his second HCT and more than 11 y after his original diagnosis.

Materials and methods
All patients described in our series were treated according to Children’s Oncology Group protocols were indicated and/or received standard of care institutional HCT protocols at our center. Informed written consent was obtained for the COG protocols and prior to each HCT. The authors obtained approval by the University of Arizona IRB board, to review the cases reported.

Discussion
Despite the advancing understanding of the role of molecular genetics in ALL and the incorporation of risk-adapted therapy upfront, 10–15% of pediatric and adolescent/young adult (AYA) patients with ALL experience a relapse.14 Historically, the outcomes of this patient population have been poor, with an event-free survival (EFS) of 30–50% in patients with first relapsed ALL in the pre CD19-directed immunotherapy era.15–17 While 51% of these individuals will achieve CR2, CR3 declined to 37% and CR4 to 31% with continued decrease in CR rates with each successive attempt.18 The 2-y EFS for patients with multiply relapsed disease is 10–40%, and strongly impacted by the total number of prior salvage attempts.16,18

In an effort to improve upon these trends, over the last 10 y, there have been significant advances in the treatment of relapsed and refractory (R/R) B-ALL which have been associated with more favorable toxicity profiles and an improved ability to achieve an MRD negative remission. More specifically, the increasing use of CD19-directed immunotherapy for early relapse, in addition to the efficacy and reliability of haplo-HCT with PT-CY, allowed patients with a previously dismal EFS to live longer lives with less long-term toxicity, and subsequently increased their ability and likelihood to pursue further therapy for subsequent relapses.8,9,19–23

Blinatumomab has become an important tool to successfully induce remission in R/R B-ALL. The Children’s Oncology Group (COG) recently completed a prospective, multicenter, phase III trial of pediatric, AYA patients with R/R B-ALL in which patients (n = 208) were randomized to receive two blocks of standard chemotherapy or two 4-week cycles of blinatumomab following a single block of re-induction chemotherapy. For the 80% of patients that remained MRD positive post re-induction block 1, 21% went on to be MRD negative after one cycle of therapy in the chemotherapy only arm, compared to 79% of those in the blinatumomab arm. Similar results were seen with the subsequent block of therapy. Overall toxicity was substantially higher in the post-induction chemotherapy arm with 61% of patients developing a grade ≥3 infection and 21% of patients developing grade ≥3 sepsis, four of which died. In contrast, only 11% and 2% of patients on the blinatumomab arm developed a CTCAEv4 grade ≥3 infection and sepsis respectively, and there were no toxic deaths. For those in the blinatumomab arm, grade ≥3 cytokine release syndrome (CRS) and seizures were seen in ≤1% of patients. Other neurotoxicity was seen in 11–14% of blinatumomab receiving patients, however all incidents were transient.1 This study exemplifies how more targeted therapy is changing the landscape of relapsed ALL. The combination of fewer and less severe toxicities, superior MRD response, and more successful bridges to transplant not only leads to an improved survival in patients receiving blinatumomab for relapse, but also allows those patients whose disease will recur in the future to be in better condition with an improved performance status when undergoing future therapies.

Another valuable CD19-directed immunotherapy that is reshaping the way we think about patients with relapsed
B-ALL is anti-CD19 CAR-T cells. A recent non-randomized phase II trial of the anti-CD19 CAR-T cell product, Tisagenlecleucel, demonstrated an MRD negative remission rate of 81% in pediatric and AYA patients with R/R B-ALL within 3 months of initial infusion. The EFS at 6 and 12 months was 73% and 50% respectively. Similar findings were demonstrated at the Children’s Hospital of Philadelphia, where 88% of patients obtained an MRD negative remission and 65% of patients remained in remission at 12 months without the addition of transplant. However, in the pediatric CAR-T cell trial at the Pediatric Oncology Branch/National Cancer Institute, 75% of MRD negative patients proceeded to HCT. At 18 months, 62% of patients who bridged to HCT were leukemia free, compared to 14% of patients who did not proceed to HCT. While grade ≥3 events did occur in 73% of patients in phase II trial utilizing tisagenlecleucel, the incidence down trended to 17% between 2 and 12 months after infusion. Among these adverse events, the most concerning nonhematologic toxicities were CRS and neurologic events, however most of the events were mitigated with supportive care measures and in some cases, cytokine blockade and no cerebral edema were reported. Similar findings have been demonstrated in adults, with lower disease burden at time of the infusion being associated with a decreased incidence of CRS and neurotoxic events, and longer survival. Neither number of prior therapies nor previous transplantation correlated with toxic effects. The initial experience with anti-CD19 CAR-T cells in a real-world setting from Center for International Blood and Marrow Transplant Research was recently published. Of 511 patients from 73 centers, 410 patients had reported follow-up data with 255 being patients with ALL. With a median follow-up of 13.4 months in ALL patients, the CR was 85.5%. The 1-y duration of response, event-free survival, and overall survival (OS) rates were similar to previous clinical trials at 60.9%, 52.4%, and 77.2%, respectively. CRS grade ≥3 was lower (16%) than previous clinical trials as patients received CAR-T therapy earlier and with less disease burden. Similarly, neurotoxicity grade ≥3 was only seen in 9% of patients.

The investigation and utilization of additional monoclonal antibody therapies targeting other B-ALL surface antigens such as CD22 with inotuzumab ozogamicin, a humanized monoclonal antibody-drug conjugate, have shown promising results. Targeting of B-ALL CD20 with rituximab or CD52 with alemtuzumab has mainly been investigated in adult B-ALL (Figure 2). Along with antibody-directed immunotherapy, the development and incorporation of TKIs into B-ALL treatment regimens have altered the prognosis of Ph+ ALL patients dramatically from <25% to approximately 80%. Ph+ ALL patients had historically been treated with HSCT as <40% were curable with chemotherapy alone. In the long-term follow-up of imatinib used in addition to chemotherapy for patients with Ph+ ALL in the COG AALL0031 study, the 5-year disease-free survival was 70% in patients receiving imatinib plus chemotherapy compared to 65% in those receiving matched sibling HCT and 59% in those receiving MUD HCT. The emergence of TKIs has led to not only improved survival, but the potential for rescuing HCT for patients in CR2.

Allo-HCT can be curative for patients with high-risk ALL. However, identification of suitable human leukocyte antigen-matched donors remains a challenge, particularly for minority groups and patients of mixed race. T cell replete haplo-HCT with PT-CY has revolutionized the field of allo-HCT. Haplo-BMT with PT-CY has emerged as the most widely applied haplo-BMT regimen, as it eliminates the need to manipulate stem cell grafts in order to prevent graft-versus-host disease (GvHD). PT-CY in haplo-BMT has been associated with relatively low rates of severe acute and chronic GvHD, graft rejection, and non-relapse mortality. Moreover, outcomes have been comparable to matched unrelated and, in some cases, matched sibling transplants. Other haplo-HCT approaches have also been successful such as depletion of αβ T-cell and B-cell depletion of the graft. The benefits of haploidentical are numerous, with arguably the most notable being that haplo-HCT extends donor availability to nearly all patients. Haplo-HCT offers additional advantages by circumventing the delays and costs associated with unrelated donor searches and hematopoietic stem cell procurement.

**Immunotherapeutics for B-ALL**

| Type                  | Agent      | Target          |
|-----------------------|------------|-----------------|
| Bispecific T cell Engagers (BITE) | Blinatumomab | CD3 → CD19     |
| Conventional CAR-T | Tisagenlecleucel | CD19          |
|                       |            | CD22*          |
| Bispecific CAR-T | Inotuzumab | CD19/CD22*     |
| Antibody drug conjugates | Rituximab | CD20           |
| Antibodies | Alemtuzumab | CD52           |

*Not FDA approved

Figure 2.
Haplo-HCT, therefore, expedites transplantation in time-sensitive circumstances such as R/R B-ALL, potentially preventing relapses while awaiting an unrelated donor. Moreover, haploidentical familial donors, especially parents, are often eager to donate and readily available for not only the initial harvest, but also potential additional collections of bone marrow, PBSCs, or donor leukocyte infusions as was the case with our second patient whose post-CAR-T cell prolonged pancytopenia was salvaged by CD34+ stem cells from her haploidentical brother. Since implementing haplo-HCT at our institution more than 80% of our alternative donor HCTs for pediatric and AYA patients with hematologic malignancies have been haploidentical with about 20% of those being second transplants. We recently updated our results reporting 84% 2-y overall survival and 74% progression-free survival.8 9 Our three cases underscore the utility of haplo-HCT in salvaging patients failing CD19-directed immunotherapy and an initial non haplo-HCT.

Alongside the advances of therapy for R/R B-ALL have come the remarkable improvements in supportive care for patients with leukemia with a focus on addressing some of the unique toxicities which have emerged in the CD19-directed immunotherapy era. The American Society for Transplantation and Cellular Therapy, for instance, has put forth comprehensive guidelines on the assessment, grading, and treatment of CRS and neurotoxicity associated with immune effector cell therapies, which has allowed for earlier recognition and more streamlined management of these toxicities.16 18 A second area of advancement which has had tremendous impact on the quality of life and outcomes of patients with acute leukemia is supportive care for infections. Multiply R/R patients and patients that are post-transplant are profoundly immunocompromised and have a high risk of severe infection, not only due to prolonged states of neutropenia, but also because the integrity of the gastrointestinal mucosa is often compromised by cytotoxic chemotherapy, and key features of serious infection may not be evident. This highlights the importance of maintaining a high clinical suspicion for infection as well as the critical need for antimicrobial prophylaxis in this patient population. While institutional practices will vary given local epidemiology and resistance rates, the IDSA/ASCO guidelines provide consensus recommendations with a goal of preventing opportunistic infections. They address the importance of antibacterial and antifungal prophylaxis during prolonged periods of neutropenia and provide guidelines on agent selection depending on the leukemia therapy being utilized.5 4 2 Our ability to optimize supportive care measurements throughout a patient’s multiply relapsed disease course plays a key role in their outcomes and ability to overcome the many toxicities that come with repeat exposure to cytotoxic chemotherapy, immunotherapy, and transplant alike.

While the idea of B-ALL being a chronic disease may have at one point seemed absurd, the advent of T cell/antibody-engaging immunotherapy has revolutionized the treatment of patients with high-risk R/R B-ALL allowing bridging to HCT with good performance status, decreased organ comorbidities and infection-free due to patients being relatively free of periods of prolonged neutropenia and advancements in supportive care. Moreover, the accessibility and reliability of haplo-HCT have made second transplants more feasible as was the case with our patients. All four of our patients are alive, obtaining their current remission (in three CR4 or greater) many years following their initial diagnosis and live high-functioning lives despite the chronicity of their disease. As a pediatric program, our report has focused on salvage treatment of B-ALL in young patients. Our findings may not be pertinent to older patients with B-ALL who inherently have a worse prognosis. Moreover, CAR-T cells have not yet been approved for B-ALL patients older than 25 y and myeloablative conditioning followed by haploidentical transplantation may not be an option for older adults with B-ALL.

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Disclosure of Conflicts of Interest

There are no conflicts of interest, financial or otherwise, involving any of the authors regarding the submission or publication of this manuscript.

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