Treatment of Relapsed/Refractory Acute Lymphoblastic Leukemia

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Keywords
Blinatumomab, chimeric antigen receptor T cell, inotuzumab ozogamicin, monoclonal antibody, relapsed/refractory acute lymphoblastic leukemia, salvage treatment

Abstract: Patients with relapsed or refractory acute lymphoblastic leukemia (R/R ALL) have dismal outcomes, with survival of less than 6 months, and treatment options in the salvage setting have been limited to conventional cytotoxic chemotherapy with minimal activity. Advances in the development of novel targeted therapies have significantly improved outcomes in R/R ALL. Blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor (CAR) T-cell therapy constitute new treatment modalities that are challenging the historical regimens and paving a new path for treating patients with R/R ALL.

Introduction

Adult acute lymphoblastic leukemia (ALL) is treated with the same multiagent chemotherapy regimens used in pediatric ALL, but they have failed to produce similar outcomes. Although these regimens induce high rates of complete remission (CR; 90%), an estimated 40% to 50% of adult patients with ALL experience relapse.[1,2] Historically, treatment options in the relapsed or refractory (R/R) setting have been limited to conventional cytotoxic chemotherapies, which result in CR rates of only 30% to 40% in first salvage and only 10% to 20% in second salvage,[3] necessitating the development of novel therapies to improve outcomes in adult R/R ALL.

Antibody-targeted therapies and chimeric antigen receptor (CAR) T-cell therapies are major breakthroughs in the management of R/R ALL. Monoclonal antibodies directed at cell surface antigens such as CD20, CD19, and CD22 function via complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, or direct phagocytosis. With nearly all precursor and mature B cells expressing CD19, and more than 90% of precursor and all mature B cells expressing CD22, blinatumomab (Blincyto, Amgen) and inotuzumab ozogamicin (Besponsa, Pfizer) are optimal antibody-targeted therapies.[4] Studies have shown significant improvement in outcomes with the use of each agent within the salvage setting, allowing better treatment options than those previously available. Furthermore, the development of CAR T cells is an innovation in the treatment of R/R ALL. This article reviews emerging therapies in treatment of R/R ALL that are challenging the current status quo.

Table 1. Blinatumomab Clinical Trial Results

Clinical Trial	Phase 2[7]	BLAST[17]	TOWER[a,9]	ALCANTARA[28]
No. of patients	189	116	271	45
Treatment setting	R/R Ph– ALL	MRD+ ALL	R/R Ph– ALL	R/R Ph+ ALL
ORR	43%[b]	NA	44%	36%[b]
CR CRh	33% 10%	NA	34% 10%	31% 4%
MRD negativity rate	82%[b]	78%[c]	76%	88%[b]
Median OS, mo	6.1	36.5	7.7	7.1

[a] Blinatumomab treatment arm

[b] Within 2 cycles

[c] At the end of cycle 1

ALL, acute lymphocytic leukemia; CR, complete remission; CRh, complete remission with partial or incomplete hematologic recovery; mo, months; MRD, minimal residual disease; ORR, objective response rate; OS, overall survival; Ph, Philadelphia chromosome; R/R: relapsed or refractory.

Philadelphia Chromosome–Negative Relapsed/Refractory ALL

Blinatumomab

Blinatumomab is a bispecific T-cell–engaging antibody (BiTE) engineered to form a synapse between CD3 T cells and CD19 B cells. This link, which bypasses the typical mechanism of the major histocompatibility complex 1 T-cell receptor complex, causes cytokine release and T-cell proliferation.[5] The cytolytic T cells then induce B-cell apoptosis through pore-forming perforins and proteases. Phase 1 studies with blinatumomab were first conducted in non-Hodgkin lymphoma, in which the drug was infused intravenously over 2 to 4 hours up to 3 times weekly.[6] However, the lack of efficacy and increased neurologic toxicity led to study termination. Owing to the dose-dependent activity, linear time-dependent clearance, and short half-life (approximately 2 hours) of blinatumomab, prolonged exposure to the drug is required for T-cell activation and B-cell depletion. Therefore, subsequent trials studied blinatumomab as a continuous intravenous (IV) infusion administered over several weeks to enhance efficacy and reduce toxicity (Table 1). Most adverse events, including cytokine release syndrome (CRS) and neurologic toxicity, occur within the first cycle as T cells are proliferating. The severity of CRS in particular is directly associated with the level of the disease burden, and CRS frequently can be managed by holding blinatumomab and administering corticosteroids.

A phase 2 confirmatory study that garnered accelerated approval for blinatumomab from the US Food and Drug Administration (FDA) was conducted in 189 patients with Philadelphia chromosome (Ph)–negative, R/R pre–B-cell ALL (Table 1).[7] Of these, 34% had experienced relapse after allogeneic stem cell transplant (alloSCT), 69% had more than 50% blasts in the bone marrow, and 39% had received at least 2 prior salvage therapies. Blinatumomab was given as a continuous IV infusion at the FDA-approved dose for a maximum of 5 cycles. Prior to initiating treatment, dexamethasone was administered to patients with a high disease burden to mitigate CRS. At a median follow-up of 9.8 months, the median overall survival (OS) was 6.1 months. A CR or CR without hematologic recovery (CRh) was achieved in 81 patients (43%) after 2 cycles. Minimal residual disease (MRD) was assessed in 73 patients, and of these, 60 (82%) became MRD-negative, which translated into longer median relapse-free survival (RFS) and median OS in comparison with those who remained MRD-positive (6.9 vs. 2.3 months and 11.5 vs. 6.7 months, respectively). AlloSCT was conducted in 32 patients (40%) who were in CR/CRh. Neurologic toxicity of grade 3 or higher occurred in 24 of the 189 patients (13%). Neutropenia (16%), anemia (14%), and febrile neutropenia (25%) were the most common grade 3 or higher adverse events. In a pooled analysis of phase 2 studies with single-agent blinatumomab that assessed the relationship between age and outcomes, the hematologic response rates in older and younger adults were similar. The rates of grade 3 or higher adverse events among younger patients (<65 years, 86%) and older patients (≥65 years, 80%) did not differ, except that the rate of grade 3 or higher neurologic events was higher in older patients (28% vs 13%).[8]

The phase 3 TOWER trial (Blinatumomab Versus Standard of Care Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia) compared blinatumomab (n=271) with investigator's choice of standard-of-care chemotherapy (n=134) in patients who

had R/R Ph-negative ALL.[9] The overall response rates were 44% and 25% (P<.001), respectively. The median OS was 4.0 months (range, 2.9-5.3 months) with standard-of-care chemotherapy vs 7.7 months (range, 5.6-9.6 months) with blinatumomab (P=.01). The median OS was also significantly superior in the blinatumomab group after censoring for alloSCT (6.9 vs 3.9 months, P=.004). Among the responders, the rates of molecular remission—defined as fewer than 10^{-4} blasts in the first 12 weeks—were 76% with blinatumomab and 48% with standard-of-care chemotherapy. An analysis of outcomes based on salvage status revealed a survival benefit for blinatumomab vs standard-of-care chemotherapy in both salvage 1 (11.1 vs 5.5 months) and salvage 2 or later (5.1 vs 3 months).[10] Grade 3 or higher adverse events occurred in 87% of the patients receiving blinatumomab and 92% of those receiving standard-of-care chemotherapy. The rates of grade 3 or higher neutropenia (57.8%), thrombocytopenia (11.9%), and infection (52.3%) were higher with standard-of-care chemotherapy, whereas neurologic events (9.4%) were more common with blinatumomab.[9]

Minimal Residual Disease. Several studies have identified MRD positivity as an independent risk factor for a poor prognosis as a consequence of higher relapse and shorter survival rates.[11-13] A meta-analysis by Berry and colleagues in 13,637 pediatric and adult patients with ALL reported longer 10-year event-free survival (EFS) in patients with MRD negativity than in those with MRD positivity (64% vs 21% in adults and 77% vs 32% in pediatric patients).[14] No differences were found between subgroups and covariates. These findings validate MRD status as a strong predictor of response and outcomes; therefore, patients should be evaluated for MRD status early in treatment because it can be used to guide treatment strategy. Blinatumomab has proved to be effective in attaining MRD negativity, allowing patients with R/R ALL to proceed to alloSCT.

Blinatumomab was first studied by Topp and colleagues in patients who achieved morphologic and hematologic remission but had persistent or reappearing MRD positivity.[15,16] Blinatumomab was given as a continuous IV infusion for 4 weeks at a dose of 15 μg/m^2 per day. The total number of evaluable patients was 20, of whom 16 (80%) achieved MRD negativity after the first cycle. After patients became MRD-negative, they were offered alloSCT if a donor was available. Interestingly, there was no difference in outcomes between those who underwent alloSCT and those who did not. With a median follow-up of 33 months, the OS rate was 60%. Most relapses occurred within 7 months after the initiation of treatment.

In the landmark BLAST trial (Confirmatory Phase II Study of Blinatumomab in Patients With Minimal Residual Disease of B-precursor Acute Lymphoblastic Leukemia), blinatumomab was studied as a single agent in 116 patients with ALL who were in MRD-positive CR.[17] Before receiving blinatumomab, 65% were in first CR and 34% were in second CR. Patients received blinatumomab at 15 μg/m^2 per day as a continuous IV infusion for 28 days every 6 weeks for up to 4 cycles. At a median follow-up of 30 months, the median OS was 36.5 months and the median RFS was 18.9 months. Of the 113 evaluable patients, 78% had a complete MRD response after cycle 1. Of note, OS was significantly longer in the patients who achieved MRD negativity after cycle 1 (39 months vs 12.5 months; P=.002). AlloSCT was offered to 67% of the patients. Among the patients in CR1 with an MRD response, alloSCT did not confer an additional survival benefit.

Gökbuget and colleagues also assessed long-term outcomes with alloSCT after blinatumomab in two phase 2 trials.[18] After approximately 3 years, 62% (16/26) of the patients 35 years or younger who received an alloSCT were alive, compared with 22% (2/9) of those who did not undergo alloSCT. Among patients older than 35 years, 40% (19/48) of those who underwent alloSCT were alive, vs 48% (13/27) of those who did not undergo alloSCT. These results suggest that alloSCT may still have a role in the management of patients in continuous complete remission after blinatumomab.

Inotuzumab Ozogamicin

Inotuzumab As a Single Agent. Inotuzumab is a CD22-directed antibody linked to calicheamicin; once released in the target cell, it causes double-stranded DNA breaks that lead to apoptosis.[19] A phase 2 study assessed the efficacy of inotuzumab in patients with R/R ALL (Table 2).[20] Inotuzumab was initiated at a dose of 1.3 mg/m^2 given by IV infusion every 3 to 4 weeks for the first 3 patients, then at a dose of 1.8 mg/m^2 by IV infusion for subsequent patients. Of the 49 patients enrolled, 73% had at least 2 prior salvage therapies and 14% had a prior transplant. After a median of 2 cycles, the overall response rate (ORR) was 57% and the median OS was 5 months. MRD negativity occurred in 63% of the patients who responded. Approximately 50% of the patients underwent alloSCT, with a median OS of 5.2 months. The most common adverse effects were infusion-related hypotension and fever. Hyperbilirubinemia and elevated liver enzyme levels occurred in 24% and 55% of the patients, respectively. Veno-occlusive disease (VOD) was the most severe adverse event, which occurred in 23% of the patients and was attributed to alkylating agent exposure as part of alloSCT conditioning regimens.

These results subsequently led to further expansion of the same phase 2 study to determine the optimal dose

Table 2. Inotuzumab Clinical Trial Results

	Inotuzumab Monotherapy			Inotuzumab With Low-Intensity Chemotherapy		Inotuzumab Plus Bosutinib[31]
Clinical trial	Phase 2[20]	Phase 2[21]	INO-VATE[a,23]	Phase 2[25]	Phase 2, Kantarjian[b,26]	Phase 1/2
No. of patients	49	41	109	59	52	16
Treatment setting	R/R Ph– ALL	R/R Ph– ALL	R/R Ph– ALL	R/R Ph– ALL	Frontline, elderly Ph– ALL	R/R Ph+ ALL[c]
Treatment schema	1.8 mg/m^2 d 1	0.8 mg/m^2 d 1 0.5 mg/m^2 d 8, 15		1.8-1.3 mg/m^2 cycle 1[d] 1.3-1.0 mg/m^2 cycles 2-4[d]		0.8 mg/m^2 d 1 0.5 mg/m^2 d 8, 15, 22
ORR	57%	59%	81%	78%	97%	81%
CR rate CRp rate CRi rate	18% 29% 10%	20% 32% 7%	36% NR 45%	59% 17% 2%	85% 10% 2%	50% NR NR
MRD negativity rate	63%	72%	78%	82%	96%	NR
Median OS, mo	5	9.5	7.7	11	Not reached	10.7

[a] Inotuzumab treatment arm

[b] Two patients with chronic myeloid leukemia in lymphoid blast crisis

[c] Inotuzumab dose was reduced after cases of VOD occurred with initial dose

[d] Phase 2 results from *Lancet Oncology*

ALL, acute lymphocytic leukemia; CR, complete response; CRi, complete response with incomplete recovery of peripheral blood counts; CRp, complete response without platelet recovery; d, day; ORR, overall response rate; MRD, minimal residual disease; NR, not reported; OS, overall survival; Ph, Philadelphia chromosome; R/R, relapsed/refractory.

and schedule of inotuzumab and minimize toxicities while preserving efficacy. The study enrolled 41 patients, and inotuzumab was given at 0.8 mg/m^2 by IV infusion on day 1, followed by 0.5 mg/m^2 by IV infusion on days 8 and 15.[21] The weekly dosing schedule yielded a median OS of 9.5 months and an ORR that was not significantly different than the every 3 to 4 weeks schedule (59% vs 57%, respectively). The weekly dosing caused less toxicity, such as pyrexia (9%) and VOD (7%), in comparison with a single dose given every 3 to 4 weeks. When the pharmacodynamics and pharmacokinetics of inotuzumab were assessed in patients with R/R ALL, the weekly dose equating to 1.8 mg/m^2 or 1.6 mg/m^2 per cycle was effective with manageable toxicities.[22] In addition, a trend of higher peak and trough concentrations of inotuzumab was observed in MRD-negative patients. Greater drug exposure over time, indicated by a larger area under the curve, was achieved with the weekly dose than with the single monthly dose, without an increase in toxicities. Therefore, subsequent studies used weekly dosing of inotuzumab.

In the phase 3 randomized INO-VATE trial (A Study of Inotuzumab Ozogamicin Versus Investigator's Choice of Chemotherapy in Patients With Relapsed or Refractory Acute Lymphoblastic Leukemia), inotuzumab (N=109) was compared with standard-of-care chemotherapy (N=109) in patients with R/R ALL who were in salvage 1 or 2.[23] Inotuzumab was given as a weekly infusion on days 1, 8, and 15 of each cycle for up to 6 cycles. The total dose was 1.8 mg/m^2 by IV infusion per cycle, then decreased to a total of 1.5 mg/m^2 as soon as CR or CR with incomplete hematologic recovery (CRi) was achieved. The CR rate and ORR were significantly higher with inotuzumab than with standard-of-care chemotherapy (36% vs 17% and 81% vs 29%, respectively; P<.0001). Responders had a higher rate of MRD negativity (78% vs 28%; P<.0001). The median progression-free survival (PFS) was 5.0 months with inotuzumab and 1.8 months with standard-of-care chemotherapy (P<.001). Median OS was 7.7 vs 6.7 months (P=.02). The 2-year survival rates were 23% and 10%, respectively. More patients

in the inotuzumab arm than in the standard-of-care chemotherapy arm proceeded to alloSCT (41% vs 11%; *P*<.001). The rates of serious adverse events did not differ between the 2 groups. Liver-related toxicities, including VOD, were more frequent in the inotuzumab arm, whereas grade 3 or higher febrile neutropenia and thrombocytopenia were more frequent in the standard-of-care chemotherapy arm. Of note, the incidence of hepatotoxicity and VOD increased with the number of prior therapies and with prior alloSCT. The rate of VOD in patients with prior alloSCT was 21%, compared with 9% in those without prior transplant, largely owing to the use of dual alkylators in the alloSCT conditioning regimen. In a post hoc analysis, the PFS, MRD negativity rate, and duration of response were similar in the patients younger than 55 years and those 55 years and older. Median OS was longer in the patients younger than 55 years than in those 55 years and older (8.6 vs 5.6 months), likely owing to the fact that a higher number of younger than of older patients proceeded to alloSCT (53% vs 27%; *P*=.0032). Further stratification by age in the patients who received inotuzumab revealed a median OS of 11.1 months in those aged 18 to 29 years and of 7.7 months in those aged 30 to 54 years. Furthermore, the incidence of VOD after alloSCT in patients treated with inotuzumab was higher in those 55 years and older than in those younger than 55 years (41% vs 17%).[24]

Inotuzumab in Combination With Low-Intensity Chemotherapy. Inotuzumab was also assessed in combination with low-intensity chemotherapy in patients who had R/R ALL to improve outcomes while minimizing toxicity. A total of 59 patients were treated with dose-modified hyper-CVAD (cyclophosphamide, vincristine, doxorubicin, dexamethasone) for 8 cycles plus inotuzumab given on day 3 of the first 4 cycles.[25] The inotuzumab dose was decreased from 1.8-1.3 mg/m^2 to 1.3 mg/m^2 during cycle 1 and to 1 mg/m^2 during cycles 2 to 4 after cases of VOD occurred with the initial doses. Dose modifications to hyper-CVAD included the following: 50% dose reduction of cyclophosphamide and dexamethasone, 75% dose reduction of methotrexate, 83% dose reduction of cytarabine, and omission of doxorubicin. After induction and consolidation, patients received either maintenance with prednisone, vincristine, 6-mercaptopurine, and oral methotrexate (POMP) or alloSCT. The 1-year RFS and OS rates were 40% and 46%, respectively. Responders had an MRD negativity rate of 82%. The benefit in patients treated in salvage 1 was greater than the benefit in those treated in salvage 2 or later; the 1-year OS rates were 57%, 26%, and 39% in salvage 1, 2, and 3, respectively (*P*=.03). AlloSCT was administered to 26 patients (44%). Those who proceeded to alloSCT in salvage 1 gained the most benefit, with a 1-year OS rate of 63%. This demonstrates the importance of using inotuzumab earlier in treatment, which is being assessed in an ongoing phase 2 study in elderly patients with newly diagnosed B-cell ALL. A total of 52 patients with newly diagnosed Ph-negative ALL and median age of 68 years received inotuzumab plus low-intensity hyper-CVD.[26] The median follow-up was 29 months and the 2-year PFS rate was 59%. VOD developed in 4 patients (8%), leading to 1 death. Some of the most common grade 3 or higher adverse events included hyperbilirubinemia (17%, n=9), thrombocytopenia (81%, n=42), infections (52%, n=27), hyperglycemia (54%, n=28), and hypokalemia (31%, n=16).

Recently, modifications to this low-intensity chemoimmunotherapy program have been made that include lower fractionated doses of inotuzumab and the addition of blinatumomab for up to 4 cycles after completion of inotuzumab.[27] The inotuzumab dose was decreased to a total of 0.9 mg/m^2 during cycle 1, given as 0.6 mg/m^2 and 0.3 mg/m^2, and to a total of 0.6 mg/m^2 in subsequent cycles, given as 0.3 mg/m^2 twice each cycle. Preliminary results from 48 patients with Ph-negative ALL in salvage 1 treated with this regimen demonstrated positive outcomes. A CR occurred in 72% (n=35). Among the patients who responded, 93% achieved MRD negativity and half were able to proceed to alloSCT. After a 31-month follow-up, the OS was 25 months and the PFS was 11 months.

Ph-Positive Relapsed/Refractory ALL

The incorporation of tyrosine kinase inhibitors (TKIs) has dramatically improved outcomes in patients with Ph-positive ALL. However, patients who relapse still have a poor OS of less than 6 months with chemotherapy plus a TKI. Therefore, new treatment modalities, such as antibody-targeted therapies alone or in combination with TKIs, are being evaluated to improve outcomes.

Blinatumomab

Blinatumomab was evaluated in patients with Ph-positive R/R ALL who either progressed on or could not tolerate a second- or later-generation TKI in the multicenter phase 2 ALCANTARA trial (Blinatumomab in Adults With Relapsed/Refractory Philadelphia Positive B-Precursor Acute Lymphoblastic Leukemia).[28] Among the 45 patients enrolled, 44% had a previous alloSCT, 38% had at least 2 relapses, and 60% had exposure to at least 2 second- or later-generation TKIs. Of note, 27% of patients had a *BCR-ABL* T315I mutation. The objective response rate was 36%. With a median follow-up of 9 months, the median OS and RFS were 7.1 and 6.7 months, respectively.

Blinatumomab was also assessed in combination with a TKI in Ph-positive R/R ALL.[29] A total of 20 patients with Ph-positive R/R ALL or chronic myeloid leukemia in lymphoid blast (CML-LBP) received blinatumomab with a second-generation TKI. The ORR was 65%. With a median follow-up of 6 months, the median OS was 14 months. Overall, the therapy was well tolerated and effective, indicating that prospective trials assessing the combination of TKIs and antibody-targeted therapies are warranted.

Bosutinib Plus Inotuzumab Ozogamicin

Patients with R/R Ph-positive ALL were included in studies of inotuzumab, specifically in the phase 1/2 trials by DeAngelo and colleagues and the phase 3 trial comparing inotuzumab with standard chemotherapy.[22,24] The outcomes of patients who had Ph-positive disease that failed to respond to prior TKIs and/or alloSCT and who were treated with inotuzumab in the above-mentioned trials were recently reported by Stock and colleagues.[30] The analysis showed that the rates of MRD negativity and CR/CRi were higher in the patients treated with inotuzumab than in those treated with standard chemotherapy, which allowed more of the former group to proceed to alloSCT. This analysis demonstrates the activity of inotuzumab in Ph-positive ALL, indicating that studies with TKIs are warranted.

Bosutinib (Bosulif, Pfizer), a second-generation TKI, was recently studied in combination with inotuzumab in 16 patients who had R/R Ph-positive ALL (n=14) or CML-LBP (n=2).[31] Inotuzumab was given at a dose of 0.8 mg/m^2 on day 1 and then 0.5 mg/m^2 weekly every 4 weeks for total of 6 cycles. Bosutinib was given at 3 dose levels: 300 (n=3), 400 (n=6), and 500 mg (n=7). Most patients were in first salvage (56%), 38% had 2 or more TKIs, and 38% had prior alloSCT. Of note, patients with T315I mutations were excluded. The treatment was well tolerated, with an ORR and a CR rate of 81% and 50%, respectively. Among the responders, 92% had a complete cytogenetic response and 85% had a major molecular response. The median OS for patients with R/R Ph-positive ALL was 10.7 months, which was markedly higher than the 6-month OS of the patients who received conventional chemotherapy.

Relapsed/Refractory T-Cell ALL

Treatment options in R/R T-cell ALL are limited and have been similar to those used in B-cell ALL. Nelarabine (Arranon, Novartis) is a T-cell–specific purine nucleoside that is demethylated to arabinosylguanine (ara-G) and then converted to arabinosylguanine triphosphate (ara-GTP), which has a greater affinity for T cells; once incorporated into the DNA, it induces apoptosis.[32] The encouraging response rates of 14% to 55% with single-agent nelarabine in phase 1 led to a phase 2 study in adult R/R T-cell ALL.[33,34] Of the 42 patients, 72% had 2 or more prior inductions and 13% had an alloSCT. Nelarabine was administered at 1.5 g/m^2 by IV infusion on days 1, 3, and 5 of a 22-day cycle. The ORR was 41% and the CR rate was 31%. The 1-year survival rate was 28%, and 4 patients proceeded to alloSCT. The most common grade 3 or higher adverse events were neutropenia and thrombocytopenia. Only 2 patients experienced neurologic toxicity, an incidence lower than that noted in the early phase 1 trial. This was thought to be due to omission of the concomitant use of intrathecal therapy and other neurotoxic chemotherapies (eg, vincristine). Early T-cell precursor ALL is categorized as a high-risk subgroup of T-cell ALL. Currently, guidance on treating this subgroup is lacking; therefore, patients are treated with chemotherapy regimens similar to those used in other T-cell ALL subtypes, but with inferior outcomes.[35]

Currently, combination therapies with venetoclax (Venclexta, AbbVie), an oral BCL-2 inhibitor, are being investigated in T-cell ALL because it is characterized by high levels of BCL-2 expression.[36-39] Venetoclax has also shown a synergistic effect with traditional ALL chemotherapies such as corticosteroids, doxorubicin, and L-asparaginase; thus, the combination of this oral agent with the backbone of ALL treatment may be advantageous and produce better outcomes.[40]

CAR T-Cell Therapy

Immune-based chimeric antigen receptor (CAR) T-cell therapy is revolutionizing the treatment of both pediatric and adult R/R B-cell ALL (Table 3). The CAR-modified T cells used for the treatment of B-cell ALL are engineered to contain an extracellular antigen domain that targets CD19 and is linked to an intracellular component (CD3ζ) and a costimulatory domain. When CAR T cells are engaged, a cytotoxic response is stimulated through the activation and proliferation of cytotoxic T cells.[41] CD28 and 4-1BB, which are among the best-studied costimulatory domains, result in a different expansion and persistence of CAR T cells. CD28 CAR T cells lead to a rapid but limited T-cell expansion, whereas 4-1BB CAR T cells display a delayed but greater T-cell expansion, prolonged persistence of CAR T cells, and consequently prolonged B-cell aplasia.[42]

The clinical activity of CD19-directed CAR T cells in R/R B-cell ALL initially achieved MRD-negative CR.[42,43] Subsequently, a phase 1/2A study of CD19-directed CAR T cells attached to the 4-1BB signaling domain (CTL019) assessed their activity in 30 patients with R/R ALL who were 5 to 60 years of age. A CR was achieved in 27 patients (90%), including 22 patients (73%) who demonstrated

Table 3. CAR T-Cell Clinical Trial Results

Costimulatory Domain	4-1BB (Maude 2014)[44]	4-1BB (Maude 2018)[45]	CD28 (Park 2018)[47]	CD28 (ZUMA)[48]
No. of patients[a]	30	75	53	16
Treatment setting	R/R pediatric and adult ALL	R/R pediatric and adult ALL	R/R adult ALL	R/R adult ALL
CR rate	90%	60%	83%	82%
Estimated EFS				
6 mo 12 mo	67% NR	73% 50%	Median 6.1 mo	N/A
Estimated OS				
6 mo 12 mo	78% NR	90% 76%	Median 12.9 mo	N/A

[a] Patients who received infusion.

ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; CR, complete remission; EFS, event-free survival; mo, months; N/A, not available ; OS, overall survival; R/R, relapsed or refractory; NR, not reported.

MRD negativity. After a median follow-up of 7 months (range, 1-24 months), the 6-month EFS rate was 67% and the OS rate was 78%. Of interest, all patients experienced CRS, which was mild to moderate in 22 patients (73%) and severe in 8 patients (27%). Severe CRS was associated with a higher baseline disease burden (P=.002) and higher peak levels of inflammatory cytokines. CRS was successfully managed with glucocorticoids and tocilizumab (Actemra, Genentech), a monoclonal antibody targeting the interleukin 6 receptor. Neurologic toxicities occurred in 13 patients (43%) and were not prevented by the use of tocilizumab.[44] The promising efficacy of CD19-directed CAR T cells attached to the 4-1BB costimulatory domain led to a phase 2 clinical trial of tisagenlecleucel (Kymriah, Novartis) in pediatric and young adult patients with R/R B-cell ALL (median age, 11 years; range, 3-23). This multicenter trial enrolled 92 patients, of whom 75 received the infusion and were evaluated for efficacy. The group had received a median of 3 prior therapies, including alloSCT in 46 patients (61%). Of note, at the time of infusion at least 15 patients were in MRD-negative CR owing to interim chemotherapy.[45] Of the 61 patients (81%) who responded, 45 (60%) achieved CR and 16 (21%) achieved CRi. All patients with a CR achieved MRD negativity. With the inclusion of all patients screened, the ORR was 66%. At a median follow-up of 13.1 months, the 6-month EFS rate was 73% and the 12-month EFS rate was 50%. The median OS was 19.1 months. The median time to maximum CAR T-cell expansion detected by qualitative polymerase chain reaction was 10 days (range, 5.7-28 days), and owing to the 4-1BB costimulatory domain, the median duration of persistence was 168 days (range, 20-617 days). All responding patients experienced B-cell aplasia, and median time to B-cell recovery was not reached. CRS occurred in 58 patients (77%) at a median of 3 days (range, 1-22 days) after the infusion and continued for an average of 8 days (range, 1-36 days). CRS was severe in 35 patients (47%), and 28 patients (37%) received tocilizumab. Neurologic toxicities occurred in 30 patients (40%). Grade 3 neurologic toxicity developed in 10 patients (13%) and was more frequent in those with grade 4 CRS (32% vs 7%). The high response rates with attainment of MRD negativity in patients with multiply R/R ALL led to the FDA approval of tisagenlecleucel in August 2017.[46]

Treatment with CD19-targeted CAR T cells and a CD28 costimulatory domain was evaluated in a phase 1 trial of 53 adult patients with R/R B-cell ALL (median age, 44 years).[47] A total of 36 patients (68%) were in salvage 3 or later, 19 patients (36%) had prior alloSCT, and 16 patients (30%) had Ph-positive R/R ALL. Of the 83 patients enrolled, 53 patients received CAR T cells and were evaluated for efficacy. At the time of T-cell infusion, approximately half of the patients had at least 5% bone marrow blasts, and 6 patients (11%) had MRD-negative disease. The CR rate was 83% (n=44), and 67% (n=32) achieved MRD negativity. For the entire cohort, the ORR was 53%. At a median follow-up of 29 months (range, 1-65 months), median EFS was 6.1 months and median OS 12.9 months. Survival was longer in the patients achieving an MRD-negative CR than in those who did not achieve MRD negativity or a CR. A total of 17 patients successfully proceeded to alloSCT.[47] Survival was significantly improved in the patients with a low burden of disease (<5% bone marrow blasts) at the time of T-cell infusion. Median EFS was 10.6 months in the patients

with a low burden of disease and 5.3 months in those with a high burden of disease (*P*=.01); median OS was 20.1 months in patients with a low burden of disease and 12.4 months in those with a high burden of disease (*P*=.02).[47] With the CD28z costimulatory domain, the median duration of CAR T-cell detection was 14 days (range, 7-138 days). CRS developed in 45 patients (85%), and was severe in 14 patients (26%). As in previous reports, a higher disease burden was associated with a higher risk for severe CRS (*P*=.004) and neurotoxicity (*P*=.002), and with shorter survival. This finding emphasizes the importance of a low disease burden at the time of CAR T-cell infusion for reduced toxicity and optimal response. Owing to the shortened activity of the CD28z costimulatory domain, this product may be best indicated as a bridge to transplant, if applicable.

Another CD19-directed CAR T-cell product manufactured with the CD28 costimulatory domain, axicabtagene ciloleucel (Yescarta, Kite Pharma), gained FDA approval for the treatment of R/R large B-cell lymphoma and is also being evaluated for the treatment of R/R B-cell ALL in the phase 1 ZUMA-3 clinical trial (A Study Evaluating KTE-X19 in Adult Subjects With Relapsed/Refractory B-precursor Acute Lymphoblastic Leukemia). Of the 16 patients who have received axicabtagene ciloleucel, 50% had at least 2 prior therapies and 19% had prior alloSCT. Severe CRS was reported in 25% of patients and severe neurologic events in 63%, requiring 94% of the patients to receive tocilizumab with or without corticosteroids. Of the 11 patients eligible for efficacy analysis, 9 achieved an objective response and all achieved MRD negativity. ZUMA-3 is ongoing, and axicabtagene ciloleucel may serve as an additional CAR T-cell product for the treatment of R/R ALL in the future.[48]

In addition to CAR T cells targeting CD19, CAR T cells targeting CD22 and novel CAR T-cell constructs, including bispecific CAR T cells targeting both CD19 and CD22 and "off-the-shelf" allogeneic CAR T cells, are currently being investigated. A phase 1 clinical trial evaluating a CD22-directed CAR T cell in 21 patients with R/R B-cell ALL, with a median age of 19 years (range, 7-30), reported a CR rate of 57% (n=12); MRD negativity was achieved in 9 patients (75%).[49] All patients had relapsed after prior alloSCT; 15 (71%) patients had previously been treated with CD19-directed CAR therapy. Grade 1 or 2 CRS developed in 16 patients (76%); no grade 3 CRS was reported. Loss of CD19 expression is a common mode of resistance to CD19-targeted CAR T cells, which was also observed with the CD22-targeted CAR.[49] Documented clinical activity with the CD22-targeted CAR has fostered the development of bispecific CAR products that simultaneously target CD19 and CD22 in an effort to prevent resistance and improve remission duration. A number of phase 1 clinical trials are currently ongoing to establish the safety and activity of CD19/CD22 bispecific CAR T cells (Table 4). The ongoing CALM (Dose Escalation Study of UCART19 in Adult Patients With Relapsed / Refractory B-cell Acute Lymphoblastic Leukemia) and PALL (Study of UCART19 in Pediatric Patients With Relapsed/Refractory B Acute Lymphoblastic Leukemia) studies are currently evaluating the safety and activity of the allogeneic CD19 CAR T UCART19 in adult and pediatric patients with R/R ALL. A total of 20 patients have received at least 1 UCART19 infusion; 16 patients were evaluated for an antileukemic response, of whom 14 (88%) achieved CR or CRi, and 12 of the 14 (86%) achieved MRD negativity. Of the 18 patients assessed for safety, CRS developed in 17 patients (94%) (grade 1-2, n=14; grade >3, n=3).[50] Allogeneic CAR T cells allow patients to bypass the barriers to autologous CAR-T products, including lymphocyte expansion and prolonged production time, and receive this novel therapy.

Conclusion and Future Directions

The development of antibody-targeted therapies and CAR T cells in R/R ALL has made possible an approach to treatment that is more effective and patient-centered than the historical standard chemotherapies. These new advances have significantly improved outcomes in the salvage setting and provided better treatment options. The future of ALL treatment appears to be the use of lower-intensity chemotherapy in combination with antibody-targeted therapies in the frontline setting to induce higher cure rates while minimizing toxicities. This strategy will also allow more patients to proceed to alloSCT. Furthermore, with the recent understanding of MRD status as an independent prognostic factor, attaining MRD negativity with the use of these agents early in treatment is necessary to improve outcomes and bridge to alloSCT. Currently, several trials are investigating optimal combinations of antibody-targeted therapies in R/R ALL: novel antibody-drug conjugates such as ADCT-402, readily available "off-the-shelf" CAR T cells, and the BCL-2 inhibitor venetoclax (Table 4).[39,51-53] As we continue to unravel and understand the pathology of this disease, it will be important to elucidate the most effective combinations and sequences of current and future targeted therapies. Limitations of the current therapies include the short half-life of blinatumomab, VOD with inotuzumab, and CRS with CAR T cells; therefore, further refinement of these agents is warranted.

Disclosures

The authors have no disclosures to report.

Table 4. Ongoing Clinical Trials Investigating Novel Treatments in Relapsed/Refractory ALL

Clinical Trial	Drug Target	Phase	Patient Population
Venetoclax			
Venetoclax and liposomal vincristine (NCT03504644)	–	1/2	R/R B-cell or T-cell ALL Ages >18 y
Venetoclax, navitoclax, and chemotherapy (NCT03181126)	–	1	R/R B-cell or T-cell ALL Ages >4 y
Monoclonal antibodies			
Daratumumab and chemotherapy (NCT03384654)	CD38	2	R/R B-cell or T-cell ALL Ages 1-30 y
ADCT-402 (NCT02669264)	CD19	1	R/R CD19+ B-cell ALL Ages >12 y
ADCT-602 (NCT03698552)	CD22	1/2	R/R CD22+ B-cell ALL Ages >18 y
CAR T-cell therapy			
NCT02315612	CD22	1	R/R CD22+ B-cell leukemia or lymphoma Ages 1-30 y
CALM (NCT02746952)	CD19[a]	1	R/R CD19+ B-cell ALL Ages 16-69 y
PALL (NCT02808442)	CD19[a]	1	R/R CD19+ B-cell ALL Ages 6 mo-17 y
PLAT-05 (NCT03330691)	CD19/ CD22	1	R/R CD19+ CD22+ B-cell leukemia or lymphoma Ages 1-26 y
NCT03233854	CD19/ CD22	1	R/R CD19+ B-cell ALL or DLBCL Ages >18 y

[a] Allogeneic CAR-T cells

ALL, acute lymphocytic leukemia; CAR, chimeric antigen receptor; DLBCL, diffuse large B-cell lymphoma; mo, months; R/R, relapsed/refractory; y, year

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