Antibody-based therapies in patients with acute lymphoblastic leukemia

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The use of multiagent combination chemotherapy regimens results in cure rates of >90% for children and ~40% for adults with acute lymphoblastic leukemia (ALL) but is associated with extensive toxicity and disappointingly low efficacy in relapsed patients. ALL blast cells express several surface antigens, including CD20, CD22, and CD19, which represent valuable targets for immunotherapy. Monoclonal antibodies, antibody–drug conjugates, and bispecific T-cell–engaging antibodies targeting these antigens offer novel mechanisms of action. Within the last several years, the anti-CD20 antibody rituximab has been added to chemotherapy for newly diagnosed patients <60 years with CD20$^+$ pre-B ALL and significantly improved the 2-year event-free survival from 52% to 65%. In adults with relapsed or refractory CD22$^+$ ALL, the antibody–drug conjugate inotuzumab ozogamicin resulted in a complete response rate of 81% and median overall survival of 7.7 months with reduced toxicity compared with standard chemotherapy. Similarly, the bispecific T-cell–engaging antibody blinatumomab yielded a complete response rate of 44% and a median overall survival of 7.7 months in an extensively treated ALL population. Moreover, ~80% of ALL patients in complete remission with evidence of minimal residual disease (MRD) achieved a complete MRD response following treatment with blinatumomab. These results highlight the tremendous promise of antibody-based treatment approaches for ALL. Ongoing and future research is critical to further define the role of the various immunotherapies in the frontline treatment of ALL. Additional challenges include the optimal sequencing of the available antibodies in the relapsed setting as well as their integration with stem cell transplant and chimeric antigen receptor T-cell therapy.

Learning Objectives

- Review the data supporting recently approved antibody-based therapies for ALL
- Review the role for antibody-based therapies to treat MRD and relapsed/refractory ALL
- Discuss how to effectively sequence treatment with novel immunotherapies in ALL

Introduction

Traditionally, the management of acute lymphoblastic leukemia (ALL) has relied on intensive multiagent cytotoxic chemotherapy followed by either prolonged maintenance or allogeneic stem cell transplantation. With this approach, >90% of children and ~40% of adults will survive, while the remaining patients succumb to their disease or treatment-related toxicity.

Approximately 80% of ALL is of the pre–B-cell origin. Several surface antigens, including CD20, CD22, and CD19, are expressed at high levels on pre–B-ALL blast cells and represent valuable targets for immunotherapy.[1] Monoclonal antibodies targeting these antigens offer novel mechanisms of action and a side effect profile distinct from chemotherapy. Current immunotherapies take advantage of antibodies through several different mechanisms, including naked antibodies, antibodies linked to cytotoxic agents, and bispecific antibodies activating T cells. Here, we discuss the recent US Food and Drug Administration (FDA) approvals of antibody-based therapies for pre-B cell ALL, including upfront therapy, minimal residual disease (MRD), and relapsed/refractory (R/R) disease (Tables 1 and 2). First, we will review the clinical benefits of the cytotoxic effects of the naked antibody rituximab. We will then address the role for the antibody–drug conjugate inotuzumab ozogamicin (IO) as well as the use of the bispecific T-cell–engaging antibody blinatumomab and their respective unique toxicity profiles. Available data suggest that the use of these immunotherapies alone or in combination with chemotherapy may result in improved outcomes. Finally, we will consider how to effectively sequence these therapies for R/R ALL, particularly in the context of available chimeric antigen receptor (CAR) T-cell therapy.

Targeting of CD20

CD20 is a B-lineage–specific antigen detected on normal and malignant cells throughout most stages of B-cell development, with the

Conflict-of-interest disclosure: M.L. is on the board of directors or an advisory committee for Pfizer; has received research funding from Amgen, BlueBirdBio, Celgene, and Pfizer; and has received honoraria and consulted for Amgen. S.D. declares no competing financial interests.

Off-label drug use: None disclosed.

Table 1. Approved uses for antibody therapy in ALL

Cell-surface antigen	Antibody therapy	Disease state	Antibody dose and schedule	Chemotherapy backbone or comparator	N (all patients)	CR (%)	MRD (%)	PFS	OS	Toxicities
CD20	Rituximab	Ph-negative newly diagnosed ALL[6]	375 mg/m^2 IV during induction, consolidation, late intensification, and maintenance for a total of 16 infusions	Vincristine, steroids, anthracycline, cytarabine, methotrexate 6-mercaptopurine, cyclophosphamide, asparaginase, etoposide	209	92	91 after first consolidation	65% 2 y EFS	71% at 2 y	Infusion reaction; hepatitis B reactivation
CD22	IO	Ph-negative and positive R/R ALL: first or second salvage[16]	Weekly IV infusion: 0.8 mg/m^2 IV on d 1, 0.5 mg/m^2 IV d 8, 15; induction = 21 d cycle, subsequent cycles if in remission 0.5 mg/m^2 d 1, 8, 15 in 28 d cycle for up to 6 cycles	Fludarabine, cytarabine, and GCSF (FLAG); high-dose cytarabine; cytarabine and mitoxantrone	326	81	78	5 mo	7.7 mo	Transaminitis, hyperbilirubinemia, VOD, thrombocytopenia
CD19	Blinatumomab	Ph-negative and positive ALL in first or later CR with MRD $\geq 10^{-3}$ after intensive chemo[25]	15 μg/m^2 daily for 28 d followed by 14 d off treatment of up to 4 cycles	None	116	NA	78	MRD responders 23.6 mo	MRD responders 38.9 mo	Fever, neurologic events
CD19	Blinatumomab	Ph-negative relapse/refractory ALL: unlimited prior salvage therapies[31]	9 μg/d, d 1-7; 28 μg/d, d 8-28; 14 d off treatment of up to 5 cycles; 28 μg/d for 4 wk on, 8 wk off × 1 y for maintenance	Fludarabine, cytarabine, and GCSF (FLAG); high-dose cytarabine; high-dose methotrexate–based regimen; clofarabine-based regimen	405	44	76	EFS, 31% at 6 mo; median DOR, 7.3 mo	7.7 mo	CRS; neurologic events

DOR, duration of remission; EFS, event-free survival; NA, not available; PFS, progression-free survival.

notable exception of plasma cells and stem cells. Approximately 30% to 50% of precursor B-cell lymphoblasts express CD20.[1] Importantly, CD20 positivity is associated with worse clinical outcome, and CD20 expression is upregulated after initiation of chemotherapy, making it an ideal target for immunotherapy.[2-4]

Rituximab is a chimeric murine/human monoclonal anti-CD20 antibody that exerts its effect through complement-dependent cytotoxicity, antibody-dependent cytotoxicity, and induction of apoptosis. In the context of ALL, rituximab has mainly been studied in combination with chemotherapy in patients with ≥20% CD20 expression. At MD Anderson Cancer Center, the addition of 8 doses of rituximab to hyper-CVAD (cyclophosphamide, vincristine, Adriamycin, and dexamethasone) was explored in almost 300 patients with newly diagnosed Philadelphia chromosome (Ph)–negative CD20$^+$ ALL. When compared with historical controls, a significant improvement in 3-year duration of response (70 vs 38%; $P < .001$) and overall survival (OS) (75 vs 47%; $P = .003$) was observed in the subgroup of patients <60 years.[5] The 07/2003 study performed by the GMALL study group (German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia) demonstrated similar results.[6] Adult CD20$^+$ pre-B ALL patients received a total of 8 doses of rituximab prior to each induction and consolidation cycle of the Berlin-Frankfurt-Münster–based regimen and were compared with patients treated on the same protocol without rituximab. In standard-risk patients, there was no difference in complete response (CR) rate (94% with rituximab vs 91% without rituximab), but a higher percentage of patients receiving rituximab achieved MRD negativity at week 16 (90% vs 59%). The probability for continuous CR and OS at 5 years remained higher in those receiving rituximab (80% vs 47% and 71% vs 57%, respectively). More recently the GRAALL study group (Group for Research on Adult Acute Lymphoblastic Leukemia) randomized newly diagnosed younger patients with Ph-negative CD20$^+$ ALL to receive intensive pediatric inspired chemotherapy with or without rituximab. Rituximab was given during all phases of therapy for up to 18 doses. The estimated 2-year event-free survival rates were significantly higher in the rituximab cohort than in the control group (65% vs 52%), confirming that rituximab in combination with chemotherapy is able to overcome the adverse prognosis of CD20 expression in younger patients with ALL.[7] Apart from infusion reactions, the risk of hepatitis B reactivation and very rare cases of leukoencephalopathy, rituximab is well tolerated. In the randomized GRAALL study, the overall incidence of severe adverse events was similar in both treatment arms. However, fewer allergic reactions to asparaginase were reported in the rituximab arm, suggesting that rituximab may enhance the therapeutic efficacy of asparaginase by reducing inactivating anti-asparaginase antibodies.[7] Combined with the inducibility of CD20 expression by steroids, this provides a rationale for evaluating the addition of rituximab to chemotherapy in patients with <20% CD20 expression.[4]

Ofatumumab is a more potent next-generation monoclonal antibody engineered to target a proximal small loop epitope of CD20 resulting in enhanced complement-dependent cytotoxicity and antibody-dependent cytotoxicity. Maiti et al[8] evaluated the addition of ofatumumab to the hyper-CVAD regimen is a phase 2 study of mostly newly diagnosed CD20$^+$ pre-B ALL patients. The combination was very effective, with 97% of patients achieving CR and 57% achieving MRD negativity at the end of induction as assessed by flow cytometry. The complete remission duration and OS rates at 2 years were 81% and 80%, respectively. Of note, the study included patients with CD20 expression of as low as 1%, and survival outcomes were independent of the percentage of CD20 expression. Based on these promising results, further evaluation of ofatumumab in patients with pre-B ALL is warranted.

Table 2. Toxicity management for antibody therapy in ALL

Antibody	Toxicity	Symptoms	Management
IO	Transaminitis Hyperbilirubinemia	Jaundice Right upper quadrant abdominal pain	Grade ≥2: Interrupt IO dosing until recovery of total bilirubin to ≤1.5× ULN and AST/ALT to ≤2.5× ULN prior to each dose unless due to Gilbert syndrome or hemolysis
IO	VOD	Jaundice Hepatomegaly Right upper quadrant abdominal pain Edema Ascites Rapid weight gain	Early detection Supportive care with diuretics and oxygen Start defibrotide 6.25 mg/kg every 6 h immediately for 21-60 d until symptoms resolve Discontinue IO permanently for all grades of VOD.
Blinatumomab	CRS	Fever, chills, hypotension, hypoxia, end-organ damage	Grade 1: Interrupt blinatumomab if fever does not resolve with acetaminophen Grade 2-3: Interrupt blinatumomab if patient cannot be supported effectively with IV fluids (requires vasopressors) and/or nasal canula oxygen. Severe cases can be treated with tocilizumab if insufficient response with interrupting blinatumomab. If symptoms resolve, patient may be rechallenged with blinatumomab at starting 9-μg/d dose. Escalate to 28 μg/d after 7 d if the toxicity does not recur. Grade 4: Discontinue blinatumomab permanently.
Blinatumomab	Neurologic events	Delirium, encephalopathy, aphasia, somnolence, tremor, seizure	Grade 3: Withhold blinatumomab until grade ≤1 and for at least 3 d, then restart blinatumomab at 9 μg/d. Escalate to 28 μg/d after 7 d if the toxicity does not recur. If the toxicity occurred at 9 μg/d, or if the toxicity takes >7 d to resolve, discontinue blinatumomab permanently. Tocilizumab will not cross the blood–brain barrier and has no utility Grade 4: Discontinue blinatumomab permanently for seizure or other event.

ALT, alanine aminotransferase; AST, aspartate transaminase; ULN, upper limit of normal.

Targeting of CD22

CD22, another antigen target in ALL, is a B-cell–specific cell-surface antigen that mediates B-cell survival, activation, proliferation, migration, and interaction with T cells and antigen-presenting cells through both ligand-dependent and independent mechanisms.[9] Typically >90% of B lymphoblasts in ALL express CD22, and it is rapidly internalized upon ligand binding, thus making it an ideal target for cytotoxic drug delivery by antibody–drug conjugates.[1] The anti-CD22 monoclonal antibody epratuzumab had limited activity as a single agent. Its effects in combination with chemotherapy have been modest in children[10,11] and adults,[12] and it is currently being studied in an international phase 3 trial (www.clinicaltrials.gov identifier NCT01802814).

IO

Unlike epratuzumab, the antibody–drug conjugate IO capitalizes upon CD22 internalization and demonstrates more robust clinical activity in ALL. IO is an anti-CD22 antibody conjugated to calicheamicin, a cytotoxic agent that cleaves double-stranded DNA. Upon antigen binding, the ALL cell endocytoses IO and the acidic environment of the lysosome dissolves the linker protein, thus releasing the calicheamicin toxin intracellularly. In vitro studies demonstrated that cells required CD22 expression for uptake of IO, but continuous saturation of the receptor was not essential for apoptosis, suggesting multiple low IO dosages may be effective.[13]

Based on safety and efficacy in lymphoma, a phase 2 trial of IO administered every 3 or 4 weeks was conducted in 49 children and adults with R/R ALL. CD22 was expressed on >50% of blasts in all patients on trial. Eighteen percent of patients achieved a CR, and 39% a CR with incomplete count recovery (CRi); however, the median duration of response was limited to 6.3 months. Although a relatively high number (33%) of patients went on to transplant, this did not provide additional survival benefit, with a median OS in all responders of 7.9 months vs a median OS in hematopoietic stem cell transplantation (HSCT) patients of 5.2 months. In addition to high rates of fever (59%) associated with drug infusion, increased levels of liver enzymes occurred in 28 (57%) patients, and 14 (28%) patients experienced increases in bilirubin concentrations.[14] An additional 41 patients were treated with IO weekly, which was equally effective (CR, CRi [neutrophils $<1 \times 10^9$/L and platelets $<100 \times 10^9$/L], and CR with incomplete platelet recovery [platelets $<100 \times 10^9$/L], 59%; median OS, 7.3 months) and less hepatotoxic than the single-dose schedule. In patients who went on to HSCT, veno-occlusive disease (VOD) was observed in 5 out of 22 (23%) with single-dose IO and in 1 out of 14 (7%) patients with weekly dose IO. Later, we will discuss further that VOD is observed more frequently in patients who receive 2 alkylating agents in the HSCT preparative regimen (5/13 patients) compared with 1 alkylating agent (1/21 patients).[15] The high

frequency of liver toxicities suggested off-target drug effects that were also observed in subsequent studies.

Another phase 2 trial that evaluated a similar IO weekly dosing regimen reported an even more impressive overall response rate of 68% (49 of 72 evaluable patients). Forty-one (84%) responders also achieved MRD negativity. This was particularly impressive, because patients were in second or later relapse.[16] The most frequent treatment-related adverse events were cytopenias and transaminitis. Median OS was 7.4 months. Given these successful results, IO was investigated in a phase 3 trial compared with standard chemotherapy in first or second salvage for Ph-negative and Ph-positive ALL. Among the 218 patients included in the intent-to-treat analysis, 81% achieved a CR or CR with partial hematologic recovery (CRh) with IO compared with only 29% of those treated with salvage chemotherapy. Additionally, rates of MRD negativity were much higher with IO than with chemotherapy (78% vs 28%, respectively).[17] When analyzing just the Ph-positive patients, the CR/CRi rate was 73% (16 of 22 patients), with 14 (64%) patients achieving an MRD-negative remission, compared with 56% and 19%, respectively, when treated with chemotherapy.[18] Despite higher rates of MRD negativity with IO, duration of remission was short in both groups (4.6 months in the IO group and 3.1 months in the chemotherapy group).[17] Progression-free survival improved significantly from 1.7 months with chemotherapy to 5.0 months with IO but was still limited. However, more patients treated with IO were able to proceed directly to HSCT (48%) than after chemotherapy (24.5%). The median OS in the IO group was 7.7 months vs 6.2 months in the chemotherapy group. In a multivariate analysis, longer duration of first remission, subsequent HSCT, MRD negativity, and attaining CR/CRi resulted in a significantly lower risk of death in IO patients compared with chemotherapy.[19] In particular, patients who achieved MRD negativity had a remarkably better median OS of 14.1 months vs 7.2 months in those who remained MRD positive.[20] Rates of serious adverse events were similar between groups. The FDA approved IO for R/R ALL in August 2017 based on high rates of remission and MRD negativity observed in this study.

The first trial investigating IO combined with low-dose chemotherapy (cyclophosphamide, vincristine, cytarabine, methotrexate, dexamethasone, or mini–hyper-CVD) and rituximab in newly diagnosed and relapsed elderly (≥60 years) ALL patients showed significant activity. Among 48 treatment-naive patients, 47 (96%) achieved a CR, CR with incomplete platelet recovery, or CRi, and 36 out of 46 patients (78%) achieved MRD negativity after 1 cycle of treatment. After 3 years of follow-up, 49% of responders remained in remission and 56% were alive. The most common grade ≥3 toxicities included infection, thrombocytopenia, and liver enzyme abnormalities.[21] This suggests that IO with chemotherapy is safe and effective in both elderly patients and newly diagnosed ALL. This is particularly important for this frail patient population who cannot typically tolerate intensive multiagent chemotherapy regimens, but it also suggests IO may play an important part in induction regimens for all age groups, particularly based on the high rates of MRD-negative remissions, which may decrease relapse rates and decrease the need for stem cell transplant in the frontline setting. The Alliance for Clinical Trials working group recently opened the A041501 phase 3 study of IO added to a pediatric-inspired intensive chemotherapy regimen in adolescents and young adults with newly diagnosed $CD22^+$ ALL. Patients are randomized to receive standard chemotherapy with or without IO, and all patients with ALL blasts expressing CD20 will also receive rituximab. The primary end point of this study is to assess if the addition of IO to chemotherapy improves survival outcomes for adolescents and young adults with ALL. The study will also evaluate the role for IO in treating MRD after induction chemotherapy.

Hepatic toxicities, including transaminitis, hyperbilirubinemia, and VOD, are the most unique adverse effects of IO. In the phase 3 trial of IO, 13% of the IO group experienced VOD (82% of cases were grade ≥3), whereas <1% of the chemotherapy group developed VOD.[22] During IO treatment or follow-up without HSCT, 5 patients in the IO group (3%) developed VOD compared with no patients in the chemotherapy group. Among the 77 patients treated with IO followed by HSCT, 17 (22%) had sinusoidal obstruction syndrome. Five VOD events after subsequent HSCT were fatal. Only 1 out of 32 patients in the chemotherapy group (3%) had (nonfatal) sinusoidal obstruction syndrome that was ongoing at the time of death due to septic shock. In a multivariate analysis, for patients treated with IO, HSCT conditioning regimens with 2 alkylating agents and last available pre-HSCT bilirubin concentration of greater than or equal to the upper limit of normal were associated with increased risk of VOD.[22] The FDA approved defibrotide to treat VOD, but the syndrome must be recognized early in order to start this in a timely manner.

Targeting of CD19

Blinatumomab

CD19 is expressed on the B-cell surface from the point of initial hematopoietic stem cell differentiation until it is downregulated during terminal differentiation into plasma cells. Importantly, B cells maintain CD19 expression after neoplastic transformation.[1] Blinatumomab is a bispecific T-cell engager that consists of an anti-CD19 antibody linked to an anti-CD3 antibody. While targeting CD19-expressing B cells, blinatumomab is able to bind and recruit CD3-expressing cytotoxic T cells, thus directing T cells to malignant B cells. Binding both CD19 and CD3 concurrently is required for T-cell activation and prevents uncontrolled cell lysis.[23] Blinatumomab was initially investigated in 20 ALL patients with MRD-positive molecularly refractory or molecularly relapsed (quantifiable MRD load of $\geq 1 \times 10^{-4}$ by polymerase chain reaction) disease. Eighty percent of patients became MRD negative, including 57% of patients who were molecularly refractory to prior chemotherapy.[24] Follow-up of this study after a median of 33 months and 5 years was significant for a hematologic relapse-free survival (RFS) of 61% and 50%, respectively.[25,26] Interestingly, 5 of 11 patients without subsequent transplant remain in remission, and 5 of 9 patients that did go on to transplant remain in remission, demonstrating the importance of MRD negativity.[26] A subsequent single-arm phase 2 study of blinatumomab evaluated 116 patients with persistent or recurrent MRD ($\geq 10^{-3}$) after a minimum of 3 blocks of intensive chemotherapy. Seventy-eight percent of patients became MRD negative. Patients who achieved MRD negativity had significantly longer RFS (23.6 vs 5.7 months) and OS (38.9 vs 12.5 months) compared with patients who had persistent MRD.[27] After at least 3 years follow-up, among patients ≤35 years, 16 out of 26 (62%) were alive after HSCT vs 2 out of 9 (22%) who did not receive HSCT; in patients >35 years, 19 out of 48 (40%) and 13 out of 27 (48%) were alive with HSCT and without HSCT, respectively. Median OS after HSCT was not reached in patients ≤35 years and was 25.7 months in those >35 years.[28] Based on these data, the FDA approved blinatumomab for MRD-positive ALL in 2018.

In R/R ALL, blinatumomab was initially investigated in patients after allogeneic stem cell transplant or those who had failed an unlimited

number of salvage therapies. Twenty-five of 36 patients (69%) achieved a CR or CRh (neutrophils >500, platelets >50 000), with the greatest proportion of responding patients receiving blinatumomab as first salvage therapy. Twenty-two (88%) of these patients achieved an MRD-negative response, with 18 patients becoming MRD negative after 1 cycle of therapy. Median OS was 9.8 months, and median RFS was 7.6 months. Thirteen responders (52%) underwent HSCT once in remission; 6 of these patients died due to treatment-related mortality, and 2 patients relapsed. Among the 12 patients who did not undergo HSCT in remission, 8 relapsed. Among the 10 relapse cases, 3 were CD19 negative (1 extramedullary), 4 were CD19 positive (2 extramedullary), and 1 was of unknown CD19 status.[29] Interestingly, lineage switch from lymphoid to myeloid leukemia at the time of relapse has also been described as a mechanism of blinatumomab resistance.[30] The subsequent larger phase 2 study included patients with primary refractory disease, patients refractory to first salvage therapy, those who relapsed within 12 months of remission, and those who relapsed after transplant. Only 43% of patients achieved a CR or CRh, which is lower than the earlier study, but this study included patients with highly refractory disease,[31] and CR/CRh was seen in high-risk groups, including patients ≥65 years (44%), those with prior HSCT (45%), and those with ≥ 3 prior salvages (34%).[32] CR or CRh occurred in more patients (73%) with <50% bone marrow blasts than those with 50% or more bone marrow blasts at baseline (29%). Eighty-two percent of responders achieved MRD negativity within the first 2 cycles of treatment. RFS was 6.9 months among MRD responders compared with only 2.3 months in MRD nonresponders. Similarly, OS was 11.5 months among MRD responders compared with 6.7 months in MRD nonresponders, which was comparable to the median OS of 6.1 months in the whole study population.[31] This once again highlights the importance of MRD negativity in ALL.

Finally, a large phase 3 study randomized Ph-negative R/R ALL patients between blinatumomab and standard-of-care salvage chemotherapy in a 2:1 fashion. Approximately 40% of patients in each group were refractory to primary or salvage chemotherapy, and the number of prior therapies was not limited for enrollment.[33] Patients treated with blinatumomab not only achieved higher rates of remission compared with chemotherapy (44% vs 25%, respectively) but also improved OS of 7.7 months compared with 4.0 months in the standard of care arm. Patients in first salvage had higher rates of remission with blinatumomab (53%) than those in second salvage (40%) or beyond (35%). However, for those who did achieve CR, rates of MRD negativity were similar regardless of number lines of prior therapy (49% in salvage 1 vs 48.5% in salvage 2 or beyond).[34] For those in salvage 2 or beyond, only 10% achieved MRD negativity with chemotherapy. The greatest survival benefit for blinatumomab was seen for patients in first salvage (11.1 months) and age <35 years (9.9 months) compared with chemotherapy (5.3 and 4.5 months, respectively). Twenty-four percent of patients in both arms were able to proceed to HSCT. After HSCT, 10 out of 38 patients in the blinatumomab group (26%) and 3 out of 12 patients in the chemotherapy group (25%) died during a median follow-up period of 206 and 279 days, respectively. Grade 3 or higher adverse events occurred at similar rates (87% blinatumomab group vs 92% chemotherapy group). The trial was stopped early due to superior outcomes observed with blinatumomab over salvage chemotherapy during the interim analysis.[33]

In a smaller phase 2 study of blinatumomab in patients with R/R Ph+ ALL who had relapsed after or were refractory to ≥1 second-generation or later tyrosine kinase inhibitor (TKI), 16 out of 45 patients (36%) achieved CR/CRh during the first 2 cycles of treatment. The responders included 4 out of 10 patients (40%) with the T315I mutation, all of whom achieved MRD-negative remissions. Responses were observed regardless of the prior number of TKI therapies including a 47% response rate in patients who had ≥3 prior TKIs. In addition, 88% of all CR/CRh responders achieved MRD negativity. Seven responders (44%) underwent subsequent HSCT. Median RFS and OS were 6.7 and 7.1 months, respectively.[35] The findings were overall similar to those reported in the randomized phase 3 trial, except that more patients in this trial achieved MRD negativity, but this did not translate into improved survival outcomes in this high-risk population.

Blinatumomab is generally well tolerated; however, its toxicity profile is remarkable for relatively rare but serious risks of cytokine release syndrome (CRS) and neurologic changes. Both events can have a wide range of symptoms. CRS most commonly presents with fever and can be associated with hypotension, hypoxia, and signs of end-organ damage depending on severity. A variety of grading systems are currently under development to assess CRS due to blinatumomab and CAR T-cell therapies.[36] In the blinatumomab arm of the phase 3 study, 4.9% of patients experienced grade ≥3 CRS and 5% of patients required dose interruption due to CRS.[33] The risk of CRS is greatest in patients with relapsed disease with high blast burden, particularly during the first treatment cycle. The phase 2 blinatumomab studies implemented several interventions to mitigate risks of CRS. First, the blinatumomab dose is lower during the first treatment week, with dose escalation to 28 μg/day for the subsequent 3 weeks if tolerated. Additionally, steroid pretreatment is recommended at a minimum within 1 hour of blinatumomab initiation and was given for up to 5 days in a phase 2 study.[31] The other phase 2 study allowed patients to receive steroids and/or cyclophosphamide 200 mg/m^2 for up to 4 days prior to blinatumomab.[29] Tocilizumab is an anti–interleukin-6 receptor antagonist that is FDA approved for treatment of CRS due to CAR T cells, but it has also demonstrated efficacy against CRS due to blinatumomab in difficult cases.[37] In order to prevent and limit CRS severity, recommendations include reducing disease burden, giving steroid premedication, incrementally escalating the dose, and considering dose interruption when symptoms arise. In addition to CRS, 9.4% of patients in the phase 3 blinatumomab trial experienced grade ≥3 neurologic events and 6% of patients required dose interruption for a neurologic event.[33] Neurologic symptoms range from delirium, encephalopathy, and somnolence to more concerning events such as seizure. All neurologic events spontaneously resolved. The pathogenesis of neurologic toxicity remains unclear. Of note, patients with ALL involving the central nervous system were excluded from all blinatumomab studies.

Based on the available data in MRD and R/R ALL, we speculate that blinatumomab treatment may be most effective in an earlier disease stage, such as MRD persistence or recurrence after first-line induction chemotherapy, decreasing the risk of relapse and possibly decreasing the number of patients who require transplant in the frontline setting. In addition to the lower leukemia burden, patients are likely to have a better performance status with a lower risk of complications. Furthermore, in more advanced disease, particularly after HSCT, the T-cell system might be negatively affected. The Eastern Cooperative Oncology Group 1910 clinical trial is evaluating the role for blinatumomab in newly diagnosed adult patients with B-cell ALL between the ages of 30 and 70 years. The study randomizes patients to receive blinatumomab during consolidation and

after intensification or to receive chemotherapy alone. Given the recent FDA approval of blinatumomab for MRD-positive ALL in 2018, the protocol has been amended to allow all MRD-positive patients to receive blinatumomab and will only randomize MRD-negative patients to receive blinatumomab and chemotherapy or chemotherapy alone (www.clinicaltrials.gov identifier NCT02003222). The Southwest Oncology Group 1318 clinical trial of blinatumomab with chemotherapy (for Ph-negative ALL) recently completed enrollment in patients ≥65 years with previously untreated disease who are unfit for intensive chemotherapy (www.clinicaltrials.gov identifier NCT02143414). Southwest Oncology Group 1318 also combines blinatumomab with dasatinib for Ph-positive and Ph-like ALL, which is still enrolling patients. The primary end points of both studies are to investigate the OS benefit of blinatumomab in frontline treatment.

Challenges: how to pick a winner

Blinatumomab and IO are some of the most exciting and promising drugs approved for R/R ALL; however, they are each limited by short duration of response and survival outcomes. This suggests that antibody-based therapies alone cannot sufficiently treat ALL, and we likely still need allogeneic stem cell transplant for curative-intent treatment in R/R ALL. Knowing that patients may progress quickly on each of these therapies, one must consider which one to give first or how to sequence the drugs. Clinical trials have not directly compared blinatumomab and IO, and the patient populations in the phase 3 R/R studies were slightly different. In particular, only salvage 1 or 2 patients were allowed in the IO study, but unlimited prior therapies were allowed in the blinatumomab study. For patients pursuing transplant, if they have low disease burden (<50% blasts), then blinatumomab should be considered for R/R disease in order to mitigate risk for CRS, increase the likelihood of response, and avoid the risk of VOD with IO. For patients with high disease burden (>50% blasts), IO appears to be more effective, and the likelihood of VOD is lower with single-agent alkylating preparative regimens for subsequent transplant. IO should be considered for patients with central nervous system involvement by ALL, because blinatumomab is contraindicated.

Antibody-based immunotherapy efficacy is greatly dependent on the percentage of blasts that express the antigen, the density of antigen expression, and ultimately the persistence of antigen expression after repeated immunotherapy exposure (Table 3). In particular, both blinatumomab and the first CAR T cells target CD19. Blinatumomab and CAR T-cell studies have both shown patients may lose CD19 expression after treatment, and this is likely a mechanism of treatment failure. Recent data demonstrated that ALL cells continue to express high levels of CD19 and can be effectively targeted with anti-CD19 CAR T cells after prior blinatumomab.[38] Overall, loss of CD19 expression is less frequently observed after blinatumomab than after CAR T-cell therapy. However, initial treatment with one therapy may ultimately leave the patient ineligible for the other therapy and vice versa. Some of this will be addressed by ongoing development of CD22-targeted CAR T cells, as well as bispecific CAR T cells that bind both CD19 and CD22. CAR T-cell studies are discussed in more detail in a separate section.[39] While CAR T cells demonstrate higher rates of MRD negativity than IO and blinatumomab in R/R ALL, they are also limited by short follow-up and durations of response. Current clinical trials are looking at retreating patients with CAR T cells or PD-1 antagonists to maintain CAR T-cell persistence and remission. The other challenge with CAR T cells is that the associated toxicity risk is greater than with blinatumomab and IO. Studies have reported nearly 100% of patients experiencing CRS and ~50% of patients experiencing neurologic toxicities. Rarely, severe CRS has resulted in coagulopathy, cerebral edema, and cerebral hemorrhage.[40-42] Elderly or unfit patients often cannot tolerate the risks of CAR T-cell therapy. Other patients cannot afford to wait several weeks for CAR T-cell manufacturing and require immediate treatment. Ultimately, the treating physician must weigh the risks and side-effect profile of each treatment against the potential clinical benefit when making a selection. Importantly, upcoming studies will examine blinatumomab vs IO vs CAR T cells for R/R ALL.

Table 3. Challenges to antibody therapy in ALL

1. Percentage of blasts that express cell surface antigen
2. Density of cell-surface antigen on ALL blast cells
3. Loss of cell-surface antigen expression after antibody-based therapy
4. With many antibody options for R/R ALL (blinatumomab, IO, and CAR T cells), how should the treatments be sequenced?
5. Are antibodies most effective in frontline disease with chemotherapy vs MRD after chemotherapy vs maintenance vs R/R disease?
6. Management of unique antibody-associated toxicities
7. Complexities of antibody administration
8. High costs of antibody therapies

Conclusion

We are fortunate to now have several antibodies to provide effective salvage therapy for patients with R/R ALL that demonstrate significantly higher response rates than traditional chemotherapy. However, as discussed above, the duration of response and survival for immunotherapies alone in R/R ALL are disappointing. The incorporation of rituximab in frontline chemotherapy and blinatumomab for MRD-positive ALL both show that the greatest likelihood of antibody-based therapies improving survival outcomes may be expected at earlier treatment stages. Ongoing and future clinical trials will determine if utilizing antibodies in newly diagnosed and MRD-positive ALL will result in significant survival differences that may change which patients are considered for allogeneic stem cell transplant.

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