Monoclonal Antibodies in Acute Lymphoblastic Leukemia

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Short Title: Monoclonal antibodies in ALL

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ABSTRACT

With modern intensive combination polychemotherapy, the complete response (CR) rate in adults with acute lymphoblastic leukemia (ALL) is 80-90%, and the cure rate 40-50%. Hence there is a need to develop effective salvage therapies and combine novel agents with standard effective chemotherapy. ALL leukemic cells express several surface antigens amenable to target therapies, including CD20, CD22, and CD19. Monoclonal antibodies target these leukemic surface antigens selectively, and minimize off-target toxicity. When added to frontline chemotherapy, rituximab, an antibody directed against CD20, increases cure rates of adults with Burkitt leukemia from 40% to 80%, and those with pre-B ALL from 35% to 50%. Inotuzumab ozogamicin, a CD22 monoclonal antibody bound to calicheamicin, has resulted in marrow CR rates of 55% and a median survival of 6-7 months when given to patients with refractory-relapsed ALL. Blinatumomab, a biallelic T-cell engaging CD3-CD19 monoclonal antibody, also resulted in overall response rates of 40-50% and a median survival of 6.5 months in a similar refractory-relapsed population. Other promising monoclonal antibodies targeting CD20 (ofatumumab, obinutuzumab), or CD19 or CD20 and bound to different cytotoxins or immunotoxins are under development. Combined modalities of chemotherapy and the novel monoclonal antibodies are under investigation.
Introduction

The estimated annual incidence of acute lymphoblastic leukemia (ALL) is 6000 cases in the United States.\textsuperscript{1} The disease spans the age continuum, with approximately 60\% of cases diagnosed in patients under the age of 20, and 11\% in patients greater than age 65.\textsuperscript{2} This makes the management of ALL complex, as patient and leukemic factors have to be considered when designing a therapeutic plan.

Multi-agent combination chemotherapy regimens for the treatment of ALL are considered a cancer success story in the pediatric setting.\textsuperscript{3} Pioneered more than five decades ago, optimization of drug combinations, doses, and sequences has offered patients who once had a dismal prognosis a cure rate of 90\%.\textsuperscript{4-5} For adults, the same magnitude of success has not been realized using similar strategies. These regimens produce high complete remission (CR) rates of 80-90\% but the cure rates are 40-50\%.\textsuperscript{6-7} Incorporation of targeted agents has improved survival and cure rates in adult ALL subsets.\textsuperscript{7-9}

Recent data have suggested that adults up to the age of 39 years may benefit from pediatric-inspired chemotherapy regimen compared with historical adult regimens.\textsuperscript{10-11} This may be due to the modifications in the common adult ALL regimens shifting away from the backbone ALL therapies applied in pediatric leukemias. However, the hyper-CVAD regimen, which kept such principles but eliminated or reduced asparaginase exposure, showed similar remission duration and survival outcomes when compared with the pediatric-inspired regimen in similar patient populations.\textsuperscript{12}
Cytotoxic chemotherapy results are modest in the setting of refractory-relapsed ALL producing CR rates of 30-40% in first salvage and 10-20% in later salvages. Few patients can be bridged to allogeneic stem cell transplantation (ASCT), 5-10% in some studies but as high as 30-40% in German trials. This bridging to ASCT offers a chance of long term remissions and cures (<20-30%).

One of the most exciting group of compounds under investigation in ALL are monoclonal antibodies that target leukemic blasts surface antigens (Figure 1). Monoclonal antibodies are designed to bind to a specific abundant target on leukemic cells, but less so expressed on normal cells. Monoclonal antibodies work through a number of mechanisms, including antibody dependent cytotoxicity, complement dependent cytotoxicity, and direct induction of apoptosis. If a target is known to internalize upon binding, potent cytotoxins can be conjugated to the antibody portion, producing an additional mechanism for leukemic targeted killing. ALL blasts targets studied most thoroughly to date include CD19, CD20, CD22, and CD52 (Table 1). The anti-CD20 antibody rituximab has produced encouraging results as a component of the initial ALL therapy of Burkitt ALL and CD20-positive pre-B ALL. This observation is interesting in itself, since single-agent rituximab has no activity in ALL. Other monoclonal antibodies targeting CD19 and CD22 are under evaluation in clinical trials of refractory-relapsed ALL. The promising results led to combining the new monoclonal antibodies with standard chemotherapy in ALL salvage and frontline regimens. Combination of different monoclonal antibodies may in the future replace components of contemporary chemotherapy regimens. Herein, we review the current status of the results achieved so far with existing and newer monoclonal antibodies in ALL.
CD20 Directed Therapy

Rituximab

The surface antigen CD20 is found on approximately 30 – 50% of the precursor B-cell lymphoblasts.\textsuperscript{16-17} Rituximab is a chimeric monoclonal antibody originally developed and approved for the treatment of non-Hodgkins lymphoma.\textsuperscript{18} Several studies have reported that the addition of rituximab to chemotherapy has improved cure rates in Burkitt ALL (Table 2).\textsuperscript{8,19-20} Two studies have shown the same for pre-B ALL.\textsuperscript{9,19}

Thomas and colleagues evaluated the addition of rituximab to the hyperCVAD regimen in newly diagnosed patients with Philadelphia-negative, CD20-positive ALL.\textsuperscript{8} Two doses of rituximab were given with each of the first four cycles of intensive chemotherapy (total 8 doses of rituximab). Rituximab was also incorporated into early and late intensification cycles (months 6 and 18 of maintenance therapy). Among patients younger than 60 years of age, the addition of rituximab improved CR duration and 3-year survival rates (75% versus 47%; \textit{P} = 0.003). The German Multicenter Study Group for ALL (GMALL) also reported an improvement in 5-year survival rates with the addition of rituximab to standard induction and consolidation chemotherapy in patients who are younger than 55 years of age.\textsuperscript{19}

Most protocols have restricted rituximab use to patients whose leukemic blast cells exhibit CD20 expression of greater than 20%. Pretreatment with corticosteroids (routinely used in ALL therapy) also upregulates CD20 expression on leukemia cells.\textsuperscript{21} Studies evaluating combined immunochemotherapy among patients with pre-B ALL and
CD20-positivity of 0-20% are warranted. Central nervous system (CNS) relapse is common in ALL. Patients who develop CNS disease have historically a poor prognosis. Phase I studies have established the safety of intraventricular rituximab in patients with primary CNS and intraocular lymphoma. An ongoing phase I/II study is testing the effectiveness of intraventricular rituximab in patients with ALL CNS relapse.

Rituximab is generally well tolerated. The most common adverse events are infusion-related and occur most frequently during or shortly after the first infusion. About 95% of these adverse reactions are mild or moderate and resolve completely after temporary interruption of the infusion. Rare cases of severe mucocutaneous reactions, hepatitis B virus reactivation, and progressive multifocal leukoencephalopathy were reported.

**Ofatumumab**

Ofatumumab is a second generation anti-CD20 monoclonal antibody that binds to a site different than rituximab. Ofatumumab targets a membrane proximal small-loop epitope on the CD20 molecule, and is more potent than rituximab. In chronic lymphocytic leukemia (CLL), ofatumumab has shown significant activity after previous rituximab exposure. In a phase II study in pre-B CD20 ALL, the combination of HCVAD with ofatumumab was found to be highly effective. Twenty-five patients with de novo pre-B CD20 positive ALL were treated. Ofatumumab was given as 2 grams twice per course in the first 4 courses. The rates of CR and minimal residual disease (MRD; by six color multiparameter flow) negativity were both 96%. With a median follow-up of 14 months,
the one-year progression-free and overall survival rates were 94% and 92%, respectively.\textsuperscript{26}

**Obinutuzumab**

Obinutuzumab is a novel glycoengineered type II CD20 monoclonal antibody which is superior to rituximab and ofatumumab in the induction of direct cell death.\textsuperscript{27} In patients with untreated CLL, treatment with obinutuzumab and chlorambucil, compared with chlorambucil alone, prolonged survival (P=0.002).\textsuperscript{28} Treatment with obinutuzumab and chlorambucil, compared with rituximab and chlorambucil, resulted in prolongation of progression-free survival (P<0.001) and in higher rates of complete response and molecular response.\textsuperscript{28} Infusion-related reactions and neutropenia were more common with obinutuzumab-chlorambucil than with rituximab-chlorambucil, but the risk of infection was not increased. Investigation of obinutuzumab in patients with CD20 positive ALL is warranted.

**CD19 Directed Therapy**

CD19 is ubiquitously expressed on B-cells. Its expression is continuous from very early stages and throughout differentiation.\textsuperscript{29} The antigen is also known to internalize upon binding of antibody, making it an attractive target for immunoconjugate therapy.

**SAR3419**

SAR3419 is a humanized monoclonal antibody linked to a semisynthetic maytansinoid compound, an antimitotic agent that binds to the same site on tubulin as vincristine.\textsuperscript{30}
Maytansinoids are far more potent than the vinca alkaloids, and development of these compounds as anticancer therapies was halted early due to excessive systemic toxicity. Selective delivery of very small doses of a maytansinoid to malignant tissue (e.g., leukemia cells), via linkage to an antibody, has renewed interest in their therapeutic potential. In preclinical models, SAR3419 significantly delayed the progression of 4 of 4 CD19 positive B-cell precursor ALL and 3 of 3 mixed lineage leukemia xenografts, induced objective responses in all but one xenograft but was ineffective against T-lineage ALL xenografts. A phase I study of SAR3419 was conducted in patients with relapsed and/or refractory B-cell lymphoma to determine the maximally tolerated dose (MTD). The dose limiting toxicity was reversible severe blurred vision, which was associated with epithelial corneal changes. The MTD was 160 mg/m² IV every three weeks. Among 39 patients treated, 74% had reductions in tumor size; one patient achieved CR. A phase II study in adults with relapsed ALL was completed.

**SGN-CD19A**

SGN-CD19A is a novel antibody-drug conjugate composed of a humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent monomethyl auristatin F (MMAF) via a maleimidocaproyl (mc) linker. Upon binding to CD19, SGN-CD19A internalizes and releases cys-mcMMAF, which binds to tubulin and induces G2/M arrest and apoptosis in the targeted cells. In a phase I dose finding study, 13 patients with relapsed or refractory B-lineage ALL (n=9) and highly aggressive lymphoma (n=4) received SGN-CD19A on Days 1 and 8 of every 21-day cycle. The starting dose was 0.3 mg/kg up and was escalated to 1.3 mg/kg per dose. No MTD was reached so far. Across all dose levels, one of the 8 (12.5%) evaluable patients with ALL
achieved CR. Adverse events of any grade were nausea (64%), fever (55%), chills (36%), and headache (27%). The study is ongoing. A second trial is evaluating SGN-CD19A every 3 weeks in aggressive B-cell non-Hodgkin lymphoma.

**Blinatumomab**

The Bispecific T-cell Engaging (BiTE) antibody blinatumomab represents the first agent in a class that redirects host T-cells to cell surface antigen-expressing cancer cells. Blinatumomab contains the variable domains of a CD19 antibody and a CD3 antibody which are joined by a non-immunogenic linker. Upon binding to CD19, the cytotoxic T cells become activated and induce cell death via the pore-forming perforin system. The drug was initially administered as an intermittent infusion two to three times weekly, but lack of activity and serious neurologic toxicity caused the schedule of administration to be abandoned. Based on the short half-life of the drug and the mechanism of action, continuous infusion over several weeks were investigated. This drastically improved the activity of the drug, particularly in ALL, and minimized adverse effects.

**Minimal Residual Disease.** The first study with blinatumomab used as continuous infusion evaluated its potential role in eradicating MRD. MRD-positivity in ALL almost universally heralds systemic relapse and confers poor prognosis. Patients treated in this study were in hematologic and morphologic CR, but had persistent or reappearing MRD during consolidation chemotherapy. Blinatumomab was given at a dose of 15 mcg/m²/day as a continuous infusion for 28 days every 6 weeks. After completing one cycle, responding patients could receive up to three additional consolidation cycles or proceed to ASCT if a donor was available. MRD conversion after one cycle was
observed in 16 of 20 evaluable patients (80%). In a long-term follow up update (median observation time 33 months), 12 of the 20 patients remained in CR. The estimated 3-year relapse-free survival was 60%. Nine patients underwent ASCT, but interestingly, non-transplanted patients had similar favorable outcome compared to the transplant group. Most relapses after blinatumomab treatment occurred early, within seven months of the start of therapy.

Within hours after start of blinatumomab infusion, a rapid T-cells redistribution was observed: after a rapid reduction, T-cells recovered immediately to pretreatment levels and expanded over baseline during the further course of the first treatment cycle. This pattern was observed in 8 of 17 evaluable patients. Although generally both CD4+ and CD8+ T-cell subpopulations participated in the increase, the subset of effector memory T-cells accounted for the major portion of expanded cells, whereas the naive T-cell subset remained essentially unchanged. This long-lasting effect of blinatumomab may be due to the amplification of cytotoxic effector T-cells induced by the anti-CD3 arm that corresponds to the proliferation induced by the cognate interaction of the specific TCR with infected target cells.

Relapsed and Refractory Disease. Blinatumomab was subsequently studied in patients with active systemic ALL relapse. The results of this ongoing trial were updated recently (Table 3). Three dose levels were explored, all involving blinatumomab administration as a continuous infusion for 28 days every 6 weeks. The overall response rate (ORR; CR or CR with incomplete count recovery) within two cycles of therapy was 69%. The estimated median survival was 9.8 months. The final dose selected for future studies was 5 mcg/m²/day during week one, and 15 mcg/m²/day
during the following three weeks. In a confirmatory open-label, single-arm, multicenter phase II study in 189 patients with relapsed-refractory disease, the ORR was 43% with 80% of the responses occurring within cycle 1. The median response duration and overall survival were 9 and 6 months, respectively (Table 3).39

The toxicity profile of blinatumomab has been largely consistent with historical studies, with fever, chills, and hypogammaglobulinemia occurring most frequently. Tremor, headache, and other mental status changes (e.g., confusion) have been reported. Fever, chills, and other constitutional symptoms are thought to be due to a cytokine release syndrome that occurs shortly after the start of therapy and are reduced with the use of steroids (e.g. dexamethasone 8-24 daily x 2-3 days). The adverse effects coincided with a rapid rise in activated T-cells after blinatumomab initiation, essentially confirming the hypothesis.40 Serious adverse events were uncommon, but seizures have been observed in both the MRD and the active disease studies. Corticosteroids before the first dose and prior to dose escalation ameliorate some of the toxicities.

Blinatumomab is currently being assessed in a phase III trial in patients with ALL in first or second relapse who are randomized to either blinatumomab or an investigator’s choice chemotherapy regimen and in a phase II study in patients with relapsed Philadelphia-positive ALL.

**CD22 Directed Therapy**
CD22 is expressed on leukemic blasts in more than 90% of patients with ALL. CD22 is rapidly internalized upon antibody binding. Receptor internalization makes it an attractive target for monoclonal antibodies conjugated to cytotoxic compounds. Possible mechanisms of action of anti-CD22 antibodies include antibody-dependent cytotoxicity, modulation of B-cell signaling, and inhibition of proliferation.

**Epratuzumab**

Epratuzumab, an unconjugated antibody directed against CD22, was studied in pediatric relapsed ALL. Patients received a “reduction” phase with single agent epratuzumab administered twice weekly for two weeks, followed by standard salvage chemotherapy combined with the antibody. With single-agent epratuzumab, most patients had stable disease, and only 1 of 15 had a partial response. Serious toxicities observed included one grade 4 seizure and one grade 3 transaminitis, neither of which occurred during the epratuzumab only phase.

In adult ALL, the Southwest Oncology Group (SWOG) has conducted a phase II study evaluating epratuzumab combined with clofarabine plus cytarabine in 31 patients experiencing first or later relapse. Epratuzumab was given IV weekly for 4 doses starting on Day 7 of therapy. Most patients were in first relapse (59%); 13% had received prior ASCT. Overall, 16 patients (52%) responded: 10 CRs and 6 CRs with incomplete recovery of neutrophils or platelets. The median survival was 5 months. Of the 16 responding patients, only 6 had MRD assessed. Of these, only 1 became MRD-negative (<0.01%); this patient survived for 11 months. While epratuzumab may have exhibited modest activity, the ideal modality for targeting CD22 might be through
utilizing antibody-conjugate therapy. Epratuzumab has recently been linked to the topoisomerase I inhibitor SN-38 and demonstrated activity against several B-cell leukemia and lymphoma cell lines.\textsuperscript{45}

\textbf{Inotuzumab ozogamycin}

The immunoconjugate directed at CD22 furthest along in development is inotuzumab ozogamycin. The antibody is linked to calicheamicin, a potent cytotoxic compound that induces double-strand DNA breaks.\textsuperscript{46} Initial studies in patients with lymphoma established an MTD of 1.8 mg/m\textsuperscript{2} IV given every 3 to 4 weeks, with reversible thrombocytopenia emerging as a frequent adverse effect.\textsuperscript{47} This led to a single institution phase II study in patients with relapsed-refractory ALL.\textsuperscript{48} The starting dose was 1.3 mg/m\textsuperscript{2} IV every 3 to 4 weeks for the first three patients; later patients received 1.8 mg/m\textsuperscript{2}. Acetaminophen, diphenhydramine, and hydrocortisone were administered to prevent infusion reactions. Forty-nine patients were treated, 73\% of whom received inotuzumab for Salvage 2 or later. The ORR was 57\%, and the median survival was 5.1 months (Table 4). Nearly half of the patients treated with inotuzumab were able to proceed to ASCT (n = 22), including four patients who were receiving their second ASCT. Survival was similar whether patients underwent subsequent ASCT or not. Transient fever and hypotension were the 2 most frequent non-hematologic adverse events, and typically occurred shortly after the inotuzumab infusion. Liver function abnormalities were also observed, but tended to be reversible. Serious toxicity in the transplant group included the development of veno-occlusive disease (VOD) in five patients (23\%). Four of the 5 patients had received multiple alkylating agents in the transplant preparative regimen, including clofarabine which may have predisposed them
to VOD. Two of the 4 patients undergoing second ASCT developed VOD, suggesting this group of patients to be also at higher risk for VOD.49

To optimize the benefit:risk of inotuzumab, a weekly dosing regimen was evaluated based on preclinical studies indicating that toxicity might be minimized while maintaining efficacy (Table 4).50 Inotuzumab was given at 0.8 mg/m² on Day 1, and 0.5 mg/m² on Days 8 and 15, every 3-4 weeks. This is the same cumulative dose per course compared with single infusion inotuzumab every three to four weeks. With the weekly regimen, ORR was similar to the single-dose schedule (59% versus 57%). The median survival was 9.5 months. The weekly regimen was less toxic. Fever of any grade occurred in 29% of patients with single-dose compared with 9% with the weekly schedule. There was also significantly less hepatotoxicity with the weekly regimen, including the incidence of VOD after ASCT (7% versus 23%). Patients receiving inotuzumab in Salvage 2 and beyond, those with high peripheral absolute blast count, and those with poor karyotype [complex; translocation (4; 11); and translocation (9; 22)] had a lower likelihood of response and shorter overall survival.

Measurements of inotuzumab levels were conducted at the end of infusion, 3 hours after the end of infusion, and on Days 7 and 8. Patients who achieved a marrow CR had lower clearance rates and higher area under the curve levels compared with patients who did not respond. Higher inotuzumab peak levels were observed with single-dose inotuzumab, but inotuzumab peak levels did not correlate with response rates.57

Additionally, 37 patients with relapsed/refractory ALL received weekly inotuzumab in a multicenter phase I/II study.51 Seventeen (46%) patients were in Salvage 1, 9 (24%) in
Salvage 2, and 11 (30%) in Salvage 3 or later. The CR and CR without count recovery rates were 79% (19/24) and 46% (6/13) in the dose expansion and dose escalation cohorts, respectively. Eighteen of the nineteen patients in the dose escalation cohort and four of the six in the dose expansion cohort achieved MRD negativity.

A randomized trial comparing inotuzumab with physician’s choice of chemotherapy in patients with ALL in first and second salvage is ongoing.

**Inotuzumab Ozogamicin in Combination with Low-Intensity Chemotherapy**

Given the promising results in the salvage studies, inotuzumab was evaluated in combination with chemotherapy. A group of patients with ALL who may particularly benefit from a more targeted regimen is elderly patients (age greater than 60 years). This group is predisposed to severe toxicity from conventional chemotherapy, which is associated with high mortality rate (30-35%) during consolidation-maintenance in CR.

Twenty-six older patients (median age of 67 years; range, 60 to 79) with newly diagnosed ALL were treated in a phase II study combining inotuzumab and low-intensity hyperCVAD therapy. The regimen eliminated doxorubicin in induction, used cyclophosphamide and steroids at 50% of the dose of previous regimens, and reduced methotrexate to 250 mg/m² on Day 1 and cytarabine to 0.5 mg/m² x4 (Days 2 and 3) of even courses. Inotuzumab 1.3-1.8 mg/m² was given once with each of the first 4 courses. The ORR was 96% [CR 79%; CR with incomplete platelet recovery (CRp) 17%]. All patients with cytogenetic abnormalities achieved complete cytogenetic response. All patients achieving response also had a negative MRD status, 75% of them after one cycle. The one-year progression-free and overall survival rates were
86% and 81%, respectively. The one-year survival rate was superior to previous results obtained with HCVAD +/- rituximab in similar patient populations (one-year survival rates 81% and 60%, respectively).

This combination was also assessed as a salvage therapy in 32 patients. The ORR was 70% (CR 50%; CRp 17%; marrow CR 3%). The 6-month progression-free and overall survival rates were 81% and 65%, respectively.\(^{52}\)

**Moxetumomab Pasudotox and BL22**

Immunotoxins are proteins that consist of two primary components: a targeting moiety for cell binding and a bacterial or plant toxin that is internalized and causes cell death. BL22 (CAT-3888) is an anti-CD22 immunotoxin composed of a variable fragment (Fv) derived from a monoclonal antibody directed toward CD22 and fused to a 38-kDa fragment of Pseudomonas aeruginosa exotoxin A (RFB4 [dsFv]-PE38).\(^{53}\) Following preclinical studies demonstrating the cytotoxic effect of BL22 against CD22+ cell lines and leukemic cells from patient samples, BL22 was also found to be highly active in phase I/II human studies in hairy cell leukemia.\(^{54}\) Wayne et al evaluated BL22 in a phase I study in childhood ALL. BL22 was administered at doses of 10 to 40 \(\mu\)g/kg every other day for three or six doses every 3-4 weeks. No dose-limiting toxicities were noted. Among 23 patients treated, 16 (70%) showed reductions of leukemic blasts; four patients had more than 2-log reductions of circulating blasts, and four patients had normalizations of peripheral blast counts. No objective CRs or partial responses were noted.\(^{55}\)
To improve the efficacy of BL22 in non-HCL tumors, further mutagenesis analysis was performed and resulted in the selection of an Fv with a higher binding affinity to surface CD22 by virtue of a slower off-rate. This new compound, initially named high-affinity BL22 (HA22), was later renamed moxetumomab pasudodotox. In a phase I study, 21 children and young adolescents with relapsed-refractory ALL received moxetumomab pasudotox every other day for six doses. Cycles were repeated every 3 weeks. Grade 3/4 capillary leak syndrome was observed in 2 of the initial 7 patients, but not after initiation of a dexamethasone pre-phase in the subsequent 14 patients. Of 17 evaluable patients, 24% achieved CR, 6% had partial response, and 47% had hematological improvement for an overall activity rate of 70%. Further clinical trials with moxetumomab administered at higher doses or increased frequency in pediatric and adult ALL are currently underway.

**CD52 Directed Therapy**

For patients with T-ALL, the development of T-cell directed monoclonal antibody therapies are lagging when compared with B-ALL. Alemtuzumab is a humanized monoclonal antibody against CD52. CD52 is expressed on 36–66% of leukemia cases, including B- and T-ALL and AML. Alemtuzumab has been investigated in small trials, but its development has been slow due to its modest activity and significant side-effects. In one series, three children with relapsed T-ALL received alemtuzumab; none responded. Additional rare CRs with CD52-positive pre-B ALL have been reported with single agent alemtuzumab. Of note, CD52 is also expressed on normal and...
malignant B-cells, though the experience using alemtuzumab in B-ALL has also been somewhat disappointing.61

Conclusions

Developments of therapeutics with monoclonal antibodies in adult ALL are highly promising. Rituximab has been shown to improve survival when combined with conventional chemotherapy. Blinatumomab and inotuzumab have demonstrated marked activity even in patients with refractory ALL. The role of monoclonal antibodies and other novel targeted approaches in adult ALL continues to be defined. Most of these agents are currently being evaluated in the setting of ALL salvage, though the most active agents will likely need to be incorporated into the frontline regimens to optimize efficacy.

With several promising compounds moving into late stages of development, the leukemia community is facing a very hopeful development in ALL. Several questions are important: 1) Can multiple available monoclonal antibodies be incorporated into one regimen? 2) Should they be combined simultaneously or sequentially, and what is the optimal sequence? 3) If regimens are designed that include multiple targeted therapies, how much chemotherapy is still needed to maintain or increase the current cure rate? 4) Will “chemotherapy” as we know it today be reserved for patients with relapsed-refractory ALL only (or patients who are prospectively predicted to benefit)? While such suggestions still appear to be hypothetical, it is plausible that incorporating active monoclonal antibodies into frontline adult ALL therapy, in a concomitant or sequential
fashion, may induce higher rates of MRD negativity and increase the cure rates to levels achieved in pediatric ALL, and may reduce the need for intensive and prolonged chemotherapy schedules.

Authorship

Contributions: E.J., S.OB., F.R., and H.K. wrote and approved the manuscript.

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**Table 1.** Targeted Therapies for Acute Lymphoblastic Leukemia

<table>
<thead>
<tr>
<th>CD20</th>
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<tbody>
<tr>
<td>Rituximab</td>
<td>When added to conventional chemotherapy, has been shown to improve survival in younger adults</td>
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<tr>
<td>Ofatumumab</td>
<td>Binds to a different epitope than rituximab, which may allow it to overcome rituximab resistant disease</td>
</tr>
<tr>
<td>Obinutuzumab</td>
<td>Novel glycoengineered type II CD20 monoclonal antibody superior to rituximab and ofatumumab in the induction of direct cell death.</td>
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<table>
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<th>CD19</th>
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<tbody>
<tr>
<td>SAR3419</td>
<td>Conjugated to a synthetic maytansinoid that is release intracellularly after antigen internalization</td>
</tr>
<tr>
<td>SGN-CD19A</td>
<td>Humanized anti-CD19 monoclonal antibody conjugated to the microtubule-disrupting agent. Upon internalization, it binds to tubulin and induces G2/M arrest and apoptosis.</td>
</tr>
<tr>
<td>Blinatumomab</td>
<td>Bispecific antibody that redirects cytotoxic T-cells to cells that express CD19</td>
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<thead>
<tr>
<th>CD22</th>
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<tr>
<td>Epratuzumab</td>
<td>Studied as part of combination therapy in adults and children with modest activity</td>
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<tr>
<td>Epratuzumab-SN38</td>
<td>Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential</td>
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<tr>
<td>Antibody Conjugate</td>
<td>Activity</td>
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<td>--------------------</td>
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<tr>
<td>Inotuzumab ozogamicin</td>
<td>Antibody conjugated to the cytotoxin calicheamicin</td>
</tr>
<tr>
<td>Moxetumomab</td>
<td>Antibody conjugated to bacterial or plant toxin</td>
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<tr>
<td><strong>CD52</strong></td>
<td></td>
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<tr>
<td>Alemtuzumab</td>
<td>Antibody that has only displayed little activity in B- and T-cell disease</td>
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**Table 2.** Activity of rituximab in patients with Burkitt leukemia

<table>
<thead>
<tr>
<th></th>
<th>MDACC(^9)</th>
<th>Germany(^{19})</th>
<th>CALGB(^{20})</th>
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<tr>
<td>Chemotherapy + Rituximab</td>
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Table 3. Activity of blinatumomab in patients with relapsed/refractory ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Pivotal Study, n=36</th>
<th>Confirmatory Study, n=189</th>
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<tr>
<td>Response</td>
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<tr>
<td>CR</td>
<td>15 (42)</td>
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<td>CR with incomplete count recovery</td>
<td>10 (28)</td>
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<td>All responders</td>
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<td>Salvage Status</td>
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<td>Salvage 2+</td>
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<tr>
<td>Median survival (months)</td>
<td>9.8</td>
<td>6.1</td>
</tr>
</tbody>
</table>

CR=complete response
**Table 4.** Activity of inotuzumab ozogamicin in patients with relapsed/refractory ALL

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Single-Dose, n=49</th>
<th>Weekly, n=40</th>
<th>Overall, n=89</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Response</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>9 (18)</td>
<td>8 (20)</td>
<td>17 (19)</td>
</tr>
<tr>
<td>CRp</td>
<td>16 (33)</td>
<td>13 (33)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>CRi, bone marrow CR</td>
<td>3 (6)</td>
<td>3 (8)</td>
<td>6 (7)</td>
</tr>
<tr>
<td>PR</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Resistant</td>
<td>18 (37)</td>
<td>14 (35)</td>
<td>32 (36)</td>
</tr>
<tr>
<td>Death &lt; 4 weeks</td>
<td>3 (6)</td>
<td>2 (5)</td>
<td>5 (6)</td>
</tr>
<tr>
<td><strong>Salvage</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salvage 1</td>
<td>13 (27)</td>
<td>16 (40)</td>
<td>29 (33)</td>
</tr>
<tr>
<td>Salvage 2+</td>
<td>36 (73)</td>
<td>24 (60)</td>
<td>60 (67)</td>
</tr>
<tr>
<td>Median survival (months)</td>
<td>5.0</td>
<td>9.5</td>
<td>6.2</td>
</tr>
</tbody>
</table>

CR=complete response; CRp=complete response without platelets recovery; CRi=bone marrow CR; PR=partial response
Figure 1. Schema of different monoclonal antibodies
Figure 1: Monoclonal Antibodies Come in Different Flavors

- CD19
- CD22
- CD20
- CD52

Unconjugated: *Rituximab, Ofatumumab, Obinutuzumab, Epratuzumab, Alemtuzumab*

Chemotoxin: *Calicheamicin, Maytansine, Auristatin*

Immunotoxin: *Diptheria, Pseudomonas*

Conjugated chemotoxin:

Bi-allelic MoAb (CD19 & CD3)
Monoclonal antibodies in acute lymphoblastic leukemia

Elias Jabbour, Susan O'Brien, Farhad Ravandi and Hagop Kantarjian