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Acute lymphoblastic leukemia in adults: encouraging developments on the way to higher cure rates

Michael S. Mathisen^{1,2}, Hagop Kantarjian², Deborah Thomas², Susan O'Brien², and Elias Jabbour²

¹Department of Pharmacy, M. D. Anderson Cancer Center, Houston, TX, USA

²Department of Leukemia, M. D. Anderson Cancer Center, Houston, TX, USA

Abstract

Conventional cytotoxic chemotherapy for adult acute lymphoblastic leukemia (ALL) is not adequate to cure most patients of the disease. Complete remission is achieved in the majority of patients, but responses are often not durable. Allogeneic stem cell transplant is used for patients with high risk features, including those who are positive for minimal residual disease after induction and consolidation therapy. Nevertheless, transplant is a toxic intervention, and does not guarantee long-term disease-free survival. Monoclonal antibodies target surface antigens present on leukemic blasts, with the aim of minimizing off-target toxicity. Rituximab, an antibody directed against CD20, prolongs the survival of younger adults with ALL when added to chemotherapy in the frontline setting. Novel agents, such as the cytotoxin–antibody conjugate inotuzumab, and the bispecific T-cell engaging compound blinatumomab, have exhibited marked antileukemic activity in the relapsed setting. As these agents continue in clinical development, it will be important to eventually incorporate them in the frontline treatment approach. We review current strategies for treating adult ALL, with a focus on novel and targeted therapies that are under development.

Keywords

Acute lymphoblastic leukemia; adult; monoclonal antibody

Introduction

The use of multi-agent chemotherapy regimens for the treatment of acute lymphoblastic leukemia (ALL) is considered a cancer success story in the pediatric setting [1]. 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 that approaches or exceeds 90% [2,3]. For adults, the same magnitude of success has not been realized using similar strategies, and the cure rate of adult ALL is estimated to be somewhere between 20 and 40% [4,5]. Adult patients tend to present with higher risk features at diagnosis, predisposing to

Correspondence: Elias Jabbour, MD, Department of Leukemia, M. D. Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 428, Houston, TX 77030, USA. Tel: 713-792-4764. ejabbour@mdanderson.org.

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chemotherapy resistance and disease relapses after initial achievement of complete remission (CR). Nevertheless, incorporation of targeted agents has led to improved overall survival (OS) for certain subsets of adult patients with the disease [5].

Monoclonal antibodies directed at cell surface antigens represent a targeted approach to cancer therapy. To date, the anti-CD20 antibody rituximab has produced encouraging results as a component of the initial treatment plan. Several of these agents are currently being evaluated in clinical trials for adult patients with relapsed ALL. The results have been promising, with the aim being to move the most effective drugs into the frontline treatment approach when leukemia cells are most susceptible to therapy. It will also be necessary to assess whether targeted therapies will be able to replace any of the components of contemporary management, or if they will be best used in combination with cytotoxic therapy. Future design of clinical trials will be important to elicit clear answers to these questions. In this review, we highlight the current approach to the management of adult ALL, with a particular focus on some of the newer therapies that appear promising in the pursuit of achieving a cure rate that rivals that of our pediatric colleagues.

Upon diagnosis, patients are stratified by a number of factors that help determine prognosis, as well as the optimal therapeutic approach. Morphology and flow cytometry are necessary to determine whether the patient has B- or T-lineage ALL. This also identifies surface markers that could represent potential treatment targets. Cytogenetic analysis is important to quickly distinguish patients whose leukemic cells harbor the Philadelphia chromosome [i.e. t(9;22)] (Ph) or other chromosomal alterations with prognostic relevance. Molecular studies are performed to uncover gene mutations that may result in aberrant pathway activation and cell survival.

Adults with a new diagnosis of ALL are treated using a similar strategy as is employed in the pediatric setting. Patients receive induction, consolidation, a prolonged maintenance phase and central nervous system (CNS) prophylaxis. The National Comprehensive Cancer Network (NCCN) has recently published guidelines for the management of ALL [6], and several regimens are endorsed [7–9]. The backbone of all accepted chemotherapy regimens includes vincristine, an anthracycline and a corticosteroid, with or without the addition of some form of L-asparaginase. Other agents that are commonly present include cyclophosphamide, methotrexate, cytarabine, 6-mercaptopurine and occasionally etoposide. Patients are generally treated according to center preference.

For patients with Ph-negative ALL, the most important factor in the selection of the initial chemotherapy regimen might be age [10]. Recent data have suggested that adult patients up to the age of 39 may benefit if they receive a pediatric-inspired chemotherapy regimen as opposed to those studied in adults [11,12]. This is presumably due to higher cumulative exposure to asparaginase, vincristine, corticosteroids and CNS directed chemotherapy administered in pediatric regimens. In a retrospective review analyzing adolescent and young adult patients (ages 16–20) over a 13-year period comparing whether they were enrolled on an adult or a pediatric protocol, outcomes were far superior for the cohort treated on pediatric studies [11]. This included a statistically significant difference in 7-year OS between the two groups (67% vs. 46%; $p < 0.001$). Notably, there was a stark difference in

baseline age between the two groups, which might explain such disparate results. Eighty-five percent of the patients in the pediatric protocol group were 16–17 years old, compared to 20% in the adult protocol group. When only considering 16–17 year olds treated on adult protocols, event-free survival (EFS) was similar to that in the group treated on pediatric protocols, although the number of patients was small.

One concern with pediatric-inspired regimens is the tolerability in patients beyond the age of 20. The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) tested the concept in patients up to the age of 60 [12]. Two hundred and twenty-five patients underwent induction, with an overall CR rate of 93.5%. After 42 months, outcomes were compared to those of a historical control group, and the pediatric-inspired regimen was found to significantly improve OS (66% vs. 44%; $p < 0.001$). However, in patients between the ages of 45 and 60, the cumulative incidence of chemotherapy-related death was 23%, essentially negating any incremental benefit offered by enhanced antileukemic activity. This prompted the authors to recommend an upper age limit of 45 for this type of approach. Intensifying the chemotherapy regimen to “pediatric strength” may only have finite capability to push the cure rate up in adult ALL, because eventually a toxicity threshold will be crossed.

Monoclonal antibody therapy may improve outcomes without substantially increasing adverse effects. The surface antigen CD20 is found on approximately 25–50% of the lymphoblasts in adult patients with precursor B-cell ALL [13,14]. This is important, as it represents a target for which commercially available drugs exist. Rituximab is a chimeric monoclonal antibody that was originally developed and approved for the treatment of various non-Hodgkin lymphomas [15]. Recently, two groups have presented or published evidence that rituximab improves OS when combined with standard chemotherapy for patients with CD20 + disease [5,16]. Thomas and colleagues evaluated the addition of rituximab to the hyperCVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate and cytarabine) in newly diagnosed patients with Ph-negative, CD20 + ALL [5]. Two doses of rituximab were given with each of the first four cycles of intensive chemotherapy (of eight cycles planned). It was also incorporated into early and late intensification cycles (months 6 and 18 of maintenance therapy). Among the patients less than 60 years of age, rituximab improved the CR duration as well as 3-year OS (75% vs. 47%; $p = 0.003$). The German Multicenter Study Group for ALL (GMALL) also reported an improvement in 5-year OS with the addition of rituximab to standard induction and consolidation chemotherapy in patients who were younger than 55 years of age [16].

Most protocols have restricted rituximab use to patients whose leukemic blast cells exhibit CD20 expression of greater than 20%. This translates to a substantial proportion of patients not able to realize the potential benefit of these agents. Pretreatment with corticosteroids has been shown to up-regulate CD20 expression on leukemia cells [17]. The concept warrants further study as an attempt to make these therapies available to a larger number of patients.

Ofatumumab is a second-generation anti-CD20 monoclonal antibody that binds to a different site compared to rituximab [18]. In chronic lymphocytic leukemia (CLL),

ofatumumab has been shown to be effective in patients who have progressed after previous exposure to rituximab [19]. Studies are ongoing to clarify ofatumumab's role as a component of frontline therapy combined with standard cytotoxic chemotherapy [20].

For patients with T-cell ALL, the treatment approach is largely similar to those in patients with B-cell ALL. Unfortunately, monoclonal antibody and other targeted approaches are not as well developed for this group. Nelarabine is a deoxyguanosine analog that selectively accumulates in T-cells, thus making it an intriguing compound for the management of T-ALL [21]. The drug is currently approved as a third-line option in pediatric and adult patients with relapsed ALL [22]. However, it may be of optimal use in the frontline setting. Jain and colleagues recently presented data evaluating nelarabine combined with the hyperCVAD regimen for newly diagnosed patients with T-ALL or T-cell lymphoblastic lymphoma (LL) ($n = 36$) [23]. Nelarabine was given either after or during consolidation chemotherapy at a dose of 650 mg/m² IV daily for 5 days. Patients enrolled in this trial achieved a CR rate of 92%, but follow-up at this point is too short for comment on whether nelarabine improves disease-free survival or OS when compared to standard chemotherapy regimens. Currently, other exciting compounds for T-ALL include the gamma-secretase inhibitors, which will be discussed in the context of salvage strategies.

Patients with Ph-positive ALL have traditionally represented a group with very poor prognosis [24,25]. Allogeneic stem cell transplant (alloSCT) has been recommended for all patients able to achieve CR as the only potentially curative approach [26]. With the evolution of the use of tyrosine kinase inhibitors (TKIs), the treatment paradigm may be shifting. Imatinib, a first-generation TKI initially developed for chronic myeloid leukemia (CML), has now been reported by several groups to have a significant impact on Ph-positive ALL when used as part of the frontline treatment approach [27–32]. Furthermore, it has also been established that a TKI should be started immediately upon recognition of Ph-positive disease, and that prolonged, continuous use is superior to pulsed or intermittent administration [29,30]. Finally, in several of the trials with adequate follow-up, alloSCT still seemed to have an influential role in long-term outcome (e.g. disease-free survival [DFS], OS) [27,28].

Second-generation TKIs (e.g. dasatinib and nilotinib) are more potent than imatinib, and are able to overcome common mutations that confer resistance to imatinib. Dasatinib and nilotinib have recently been shown to be superior when used first-line to treat CML [33,34]. Dasatinib is approved as a single agent as salvage therapy for Ph-positive ALL [35], but is only able to produce transient remissions when employed as monotherapy. Because of the results observed using imatinib, dasatinib has been combined with chemotherapy as initial treatment. Ravandi and colleagues administered dasatinib 100 mg daily for 14 days with each cycle of hyper-CVAD chemotherapy (planned eight cycles) [36]. After the induction and consolidation rounds, patients would go on to receive dasatinib 100 mg daily on a continuous basis as part of maintenance therapy. Thirty-five patients were enrolled, and 33 (94%) achieved a CR. With short follow-up, the 2-year OS was 64%. Very few patients proceeded to alloSCT in first CR, and longer follow-up will be necessary to establish whether dasatinib combined with chemotherapy obviates the need for upfront transplant in all patients. The regimen was subsequently amended, calling for continuous dasatinib dosing

starting with the commencement of cycle 2 at a dose of 70 mg. This strategy may further improve the outcome.

Intensive chemotherapy with TKIs is highly effective, but can be toxic, and several groups have attempted to reduce the overall exposure to cytotoxic chemotherapy. The goal is to maintain high remission rates while minimizing induction-related mortality and deaths in CR. This concept has been explored using imatinib and the second-generation TKI dasatinib [37,38]. In the GRAAPH-2005 study, 265 evaluable patients (between ages 18 and 60) were randomized to imatinib 800 mg daily for 28 days combined with weekly vincristine and dexamethasone versus imatinib 800 mg daily on days 1–14 combined with hyperCVAD chemotherapy [37]. Patients received similar consolidation, and the ultimate plan was for all patients to receive an alloSCT or an autologous SCT (autoSCT). The CR rate after induction was higher in the low intensity group, mainly due to excess induction related mortality in the hyperCVAD group (7% vs. <1%; $p = 0.01$). An equal number of patients in each group proceeded to autoSCT and alloSCT. At 3 years, OS was similar between the two cohorts (53% for low intensity vs. 49% for hyperCVAD; $p = 0.61$).

In an update to the EWALL-Ph-01 study, Rousselot and colleagues presented data using dasatinib and low intensity chemotherapy in an elderly group of patients (age 55 and older) with newly diagnosed Ph-positive ALL [38]. Seventy-one patients were enrolled and received induction with dasatinib 140 mg once daily combined with vincristine and dexamethasone. Consolidation therapy included dasatinib 100 mg once daily continuously combined with methotrexate and asparaginase alternating with cytarabine. Five patients subsequently underwent alloSCT. The estimated OS at 3 years for the entire cohort was 45%. Several patients developed point mutations within the tyrosine kinase domain at the time of relapse. Mutations at T315I, known to confer resistance to most commercially available TKIs, represented the majority of cases. This underscores the fact that resistant disease can still emerge under treatment with second-generation TKIs, and there is a need for options in patients who develop these mutations.

Ponatinib is a novel TKI that was molecularly designed to overcome most known BCR–ABL mutations, including the T315I [39,40]. A phase I trial was recently conducted to establish the maximum tolerated dose (MTD) in patients with refractory Ph-positive malignancies [41]. Of the patients with advanced disease (which included accelerated and blast phases of CML), the response rate was noted to be 36%. The dose-limiting toxicities were found to include elevated pancreatic enzymes, clinical pancreatitis and rash. The recommended dose for the phase II trial was 45 mg once daily. An update to the phase II PACE trial was recently presented, which enrolled 449 patients, including 94 with blast phase CML or Ph-positive ALL [42]. Overall, 34% of the patients in this group responded, and there appeared to be similar response rates between those patients with resistance or intolerance to other TKIs who did not have the T315I mutation. Based on these results, ponatinib was granted accelerated approval for patients with Ph-positive ALL. Ongoing studies will be aimed at clarifying ponatinib's role in the frontline setting when combined with chemotherapy.

Role of stem cell transplant

Patients with high risk features at diagnosis are typically recommended to undergo alloSCT in first CR, given the availability of a suitable donor. The definition of high risk ALL varies between studies, but most include Ph-positive disease, chromosomal translocations involving the mixed lineage leukemia gene [e.g. t(4;11)], elevated white blood cell count (greater than $30 \times 10^9/L$ for B-ALL, or $100 \times 10^9/L$ for T-ALL) and hypodiploidy. Recently, a large study found that patients with standard risk ALL (i.e. the absence of high risk features) benefited from alloSCT in first CR, while those with high-risk disease did not benefit [43]. This has caused considerable debate regarding which patients should be referred for this intervention. Most clinicians find it unreasonable to transplant every patient with ALL in first CR, as a significant proportion will possibly be cured with chemotherapy alone. Of note, patients with standard risk disease might have not received optimal induction therapy.

Perhaps the most important prognostic marker is the presence or absence of minimal residual disease (MRD) [44]. Bassan and colleagues used MRD status at various time points after CR had been attained to guide treatment in adult patients with ALL [45]. Patients could be reassigned to a higher risk group if they remained MRD positive at the end of consolidation, and this group was dispositioned to alloSCT rather than the prolonged maintenance phase. MRD was the most important prognostic factor when taking all known clinical factors also into account. Patients who achieved MRD-negative status had a significant improvement in 5-year OS (75% vs. 33%; $p = 0.001$).

These data suggest that the decision to perform alloSCT in first CR should be individualized based on a number of factors. For high risk patients, especially in younger adults, most centers continue to recommend alloSCT in first CR if there is an appropriate donor. For standard risk patients, MRD information should be incorporated into post-remission treatment planning. Those positive for MRD can be reassigned to a higher risk category, and this subset of patients may benefit most from a transplant in first CR.

Salvage therapy

Despite an exceptionally high rate of initial CR, most adult patients with ALL will relapse. Current strategies to induce a second remission translating into long-term survival are lacking. In the large, international Medical Research Council (MRC) UKALL12/Eastern Cooperative Oncology Group (ECOG) 2993 trial, data on relapse and the subsequent clinical course were published, and included 609 patients [46]. The median survival of patients after relapse was 24 weeks, with 5-year OS being only 7%. Patients who experienced a first CR duration of greater than 2 years fared slightly better, with a 5-year OS of 11%. Kantarjian and colleagues also reported a large cohort of relapsed patients with short duration of first CR, and median OS was less than 5 months [47]. These data underscore the need for improving remission durability. Also, better salvage options for patients who relapse are warranted. Patients with relapsed ALL should be considered for enrollment in clinical trials. For those who are ineligible, therapy is selected based on previous treatment, duration of first remission, performance status, organ function and cytogenetic/molecular information.

The goal of salvage therapy is to achieve a second CR with the hope of consolidating with an alloSCT.

While approved as a third-line option as a single agent for pediatric patients, clofarabine has been used as a single agent or in combination for adults. Combination approaches with clofarabine as a component have been evaluated. Etoposide and cyclophosphamide were combined with clofarabine and administered to a group of heavily treated pediatric patients ($n = 25$) [48]. The overall response rate in this study was 44%, and 10 of the 25 patients were subsequently able to move to alloSCT. One concern after initial enrollment was a high rate of veno-occlusive disease (VOD) in patients who had received previous alloSCT, and the protocol was amended to exclude these patients going forward. Subsequently, no additional cases of VOD were diagnosed.

Taken from the pediatric experience, several groups have evaluated the role of clofarabine in adults. The Spanish group conducted a retrospective review in 31 patients who received clofarabine-containing chemotherapy in 17 centers around the country [49]. Eighty-five percent of the patients had received two or more previous therapies. Patients received clofarabine as a single agent, combined with cyclophosphamide, combined with etoposide and cyclophosphamide or combined with cytarabine. The overall response rate was 35% (including one partial responder), and six of the 11 were able to be bridged to an alloSCT. Seven of 31 (23%) of the patients died in the neutropenic phase and were unable to be assessed for response. At 12 months, the probability of OS was 10%. French investigators have also explored multiple combination regimens that include clofarabine [50].

An augmented version of the hyperCVAD regimen was developed for patients with a good performance status who are candidates for multi-agent chemotherapy [51]. Patients received hyperCVAD with intensified doses of dexamethasone and vincristine. Pegylated asparaginase was added to enhance antileukemic activity. The regimen was studied in 88 evaluable patients in first or greater relapse, 80% of whom had received prior therapy with standard hyperCVAD. Forty-seven percent of the patients achieved a CR, and the median OS for the entire cohort was 6 months.

The GMALL group studied nelarabine in a group of relapsed and/or refractory adult patients with T-ALL or T-LL ($n = 126$), administering 1500 mg/m^2 on days 1, 3 and 5 with an objective of testing the realization of alloSCT after treatment [52]. Most patients (74%) were refractory to their most recent chemotherapy regimen, and 21% were status post-alloSCT. The overall response rate was reported to be 46%, with 36% of patients achieving CR. Of the 45 patients who achieved a CR, 80% were able to proceed with some form of transplant (mostly alloSCT with one patient undergoing autologous SCT). Patients in CR who went to transplant had a 3-year probability of survival of 36%. Nelarabine was well tolerated, with grades 1–2 neurologic toxicity and hepatic toxicity being observed most frequently. Of note, several patients with a partial response (PR) were converted to CR status after receiving subsequent cycles. The authors recommend giving all patients at least two cycles in the absence of clear progression or prohibitive toxicity.

Vincristine is almost universally used in frontline treatment regimens for both adult and pediatric ALL. Nevertheless, cumulative exposure to vincristine can lead to debilitating and sometimes irreversible peripheral neuropathy, making it necessary to cap the dose at 2 mg flat. A liposomal formulation of the drug was devised as an attempt to optimize exposure to leukemic cells while minimizing known toxicities. Vincristine sulfate liposome was tested in a phase I study to determine the MTD [53]. Subsequently, a large, single arm, phase II study was designed for patients in second or greater relapse [54]. Patients received a weekly infusion of the liposomal vincristine at a dose of 2.25 mg/m². Importantly, there was no dose capping in this trial, and patients were allowed to enter if they had existing mild or non-persistent peripheral neuropathy. Sixty-five patients were enrolled, 100% of whom had been previously exposed to conventional vincristine. More than 50% of the patients had received three or more previous therapies for ALL. The overall response rate, including partial responders and patients who failed to recover their peripheral counts, was 35%. Twelve patients were able to be moved to an alloSCT, and the median OS in the entire cohort was 4.6 months. Conventional vincristine is often regarded as being non-myelotoxic. Interestingly, grades 3 and 4 neutropenia were seen with the liposomal preparation. This may reflect a combination of increased drug exposure, with the fact that most of these patients were heavily pretreated with cytotoxic chemotherapy. The results of this study led to the approval of vincristine sulfate liposome as a third-line agent for ALL in 2012.

Novel agents and potential targets

It is clear that cytotoxic chemotherapy is not a highly successful strategy for adults with relapsed ALL. Some patients are able to be bridged to alloSCT, but this in itself often fails to lead to long-term remissions. Several monoclonal antibodies designed to target cell surface antigens on leukemic cells are being tested in the clinic, with very promising results (Table I). These agents are being used both as single agents and in combination approaches. Other targets include aberrant surface or cytoplasmic kinases that might be targeted by existing or experimental small molecules.

CD19 directed therapy

CD19 is ubiquitously expressed on B-cells, and the expression is continuous from the very early stage and throughout differentiation [55]. The antigen is also known to internalize upon binding of antibody, making it an attractive target for immunoconjugate therapy (CCR). SAR3419 is a humanized monoclonal antibody linked to a semisynthetic maytansinoid compound. The maytansinoids are a group of antimitotic agents that bind to the same site on tubulin as does vincristine [56]. However, they are far more potent than the vinca alkaloids, and development of these compounds as anti-cancer therapies was halted early due to excessive systemic toxicity. The ability to deliver a very small dose of a maytansinoid specifically to malignant tissue (e.g. leukemia cells) via linkage to an antibody has renewed interest in their therapeutic potential. A phase I study of SAR3419 was conducted in patients with relapsed and/or refractory B-cell lymphoma to determine the MTD ($n = 39$) [57]. Patients received doses ranging from 10 to 270 mg/m² IV every 3 weeks. The dose limiting toxicity was reversible severe blurred vision, which was associated with epithelial corneal changes. The MTD was established at 160 mg/m² IV every 3 weeks.

In terms of tumor response, 74% of patients experienced a reduction in tumor size, with one patient meeting the definition of CR. There is currently an ongoing phase II study in adults with relapsed ALL [58].

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 [59]. 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 [59]. Based on the short half-life of the drug and the mechanism of action, investigators began using continuous IV infusion over several weeks, which drastically improved activity of the drug and minimized adverse effects.

The first major study was published by the GMALL group and evaluated blinatumomab and its potential role in eradicating MRD [60]. Patients on this study were in hematologic and morphologic CR with persistent or reappearing MRD during consolidation chemotherapy. Of note, MRD-positivity in ALL almost universally heralds a systemic relapse and confers a very poor prognosis in general. Blinatumomab was given at a dose of 15 $\mu\text{g}/\text{m}^2/\text{day}$ as a continuous infusion for 28 days followed by a 14-day break [60]. After completing one cycle, responding patients could receive up to three additional consolidation cycles or move to alloSCT if a donor was available. MRD conversion after one cycle was achieved in 16 out of 20 evaluable patients (80%). Recently, the long-term follow-up was published for patients enrolled in this protocol [61]. The endpoint analyzed was relapse-free survival (RFS) with a median observation time of 33 months. Overall, 12 of the 20 patients remained in CR, which translated to a RFS estimate of 60%. Nine patients went on to receive alloSCT, though the authors stated that non-transplanted patients did not appear to have an inferior outcome compared to the transplant group. Most relapses after blinatumomab treatment occurred early, within 7 months of the start of therapy. After this time point, there has been little or no hematologic relapse in the non-transplanted responders.

Blinatumomab was subsequently studied in patients suffering a systemic ALL relapse, and the results of this ongoing trial were updated recently [62]. The GMALL group explored three dose levels, all involving the drug being administered as a continuous infusion for 28 days followed by a 14-day rest period. The overall response rate (CR or CR with incomplete count recovery) within two cycles of therapy was 68%. The final dose selected to move forward was 5 $\mu\text{g}/\text{m}^2/\text{day}$ during week 1, and 15 $\mu\text{g}/\text{m}^2/\text{day}$ during the following 3 weeks.

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 deviations (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. The adverse effects were recently found to coincide with a rapid rise in activated T-cells after blinatumomab initiation, essentially confirming the hypothesis [63]. Serious adverse events have been uncommon, but reversible seizures have

been observed in both the MRD and the relapsed studies. Corticosteroids before the first dose and prior to dose escalation may ameliorate some of the toxicity, and studies will be necessary to confirm whether a “cytokine spike” correlates with response and other outcomes.

Another approach to selectively targeting CD19 positive cells involves the use of chimeric antigen receptor T-cells. These are autologous T-cells genetically engineered to express antibody against the surface marker. Recently, this strategy was employed in a patient with refractory CLL [64]. Re-infusion of the modified cells led to a delayed tumor lysis syndrome, and subsequently morphologic and cytogenetic remissions were documented. Of note, the cells expanded and persisted in the patient’s blood for up to 6 months.

CD22 directed therapy

CD22 is expressed on leukemic blasts in more than 90% of patients with ALL [14]. Another key feature is the rapid internalization of the receptor upon antibody binding [65]. Possible mechanisms of action of anti-CD22 antibodies include antibody-dependent cytotoxicity, modulation of B-cell signaling and inhibition of proliferation [66]. Further, receptor internalization makes it an attractive target for monoclonal antibodies conjugated to cytotoxic compounds.

Epratuzumab is an unconjugated antibody directed against CD22, as was studied in pediatric patients experiencing relapsed ALL by the Children’s Oncology Group (COG) [67]. Patients received a “reduction” phase with single-agent epratuzumab administered twice weekly for 2 weeks, followed by standard salvage chemotherapy combined with the antibody. When considering the activity of the single agent, most patients had stable disease, and one of 15 met the definition of a partial response (assessed at the end of the “reduction” phase). Epratuzumab was well tolerated, with first dose infusion reactions occurring most frequently. Of note, prophylactic acetaminophen and diphenhydramine were given to prevent infusion reactions, and perhaps the premedication regimen could be modified to further reduce the incidence. Serious toxicities observed included one grade 4 seizure and one grade 3 transaminitis, neither of which occurred during the epratuzumab-only phase.

In adults, the Southwest Oncology Group (SWOG) is conducting a phase II study evaluating epratuzumab combined with clofarabine plus cytarabine in patients experiencing first or greater relapse [68]. This study was recently presented in abstract form, and results were available for 32 patients. Epratuzumab was given at a dose of 360 mg/m² IV weekly for four doses starting on day 7 of therapy. Most patients were in first relapse (59%), and 13% had received prior alloSCT. Overall, there were 13 responders, eight CRs and five CRs with incomplete recovery of neutrophils or platelets. The median OS was reported to be 4 months. While epratuzumab appears to exhibit modest activity, the ideal modality for targeting CD22 might be through utilizing antibody-conjugate therapy. Indeed, epratuzumab has recently been linked to the topoisomerase I inhibitor SN-38, and demonstrated activity against several B-cell leukemia and lymphoma cell lines [69].

The immunoconjugate directed at CD22 furthest along in development is inotuzumab ozogamicin (formerly CMC-544). The antibody is linked to calicheamicin, a very potent

cytotoxic compound that induces double-strand DNA breaks [70]. Initial studies in patients with lymphoma established an MTD of 1.8 mg/m² IV given every 3–4 weeks, with reversible thrombocytopenia emerging as a frequent adverse effect [71]. This led to a single-institution phase II study in patients with relapses and/or refractory ALL [72]. The starting dose was 1.3 mg/m² IV every 3–4 weeks for the first three patients, but most patients received the 1.8 mg/m² dose as was given in the lymphoma study. Acetaminophen, diphenhydramine and hydrocortisone were administered to prevent infusion reactions. In patients who failed to respond after cycle 2 whose leukemic blasts also expressed CD20, the addition of rituximab was permitted. Forty-nine patients were treated, 73% of whom were receiving inotuzumab as salvage therapy two or higher. The overall response rate was 57%, and median OS for the entire cohort of patients was 5.1 months. Survival was similar whether patients underwent subsequent alloSCT or not. Transient fever and hypotension were two of the most frequently reported non-hematologic adverse events, and typically occurred shortly after the inotuzumab infusion. Liver function abnormalities were also observed, but tended to be reversible. Nearly half of the patients treated with inotuzumab were able to proceed to alloSCT ($n = 22$), including four patients who were receiving their second alloSCT. Serious toxicity in the transplant group included the development of VOD in five patients (23%). Many of these patients had received multiple alkylating agents in the transplant preparative regimen (e.g. thiotepe and melphalan, thiotepe and busulfan), which may have caused a predisposition to VOD. Clofarabine was also used in a number of patients, which is a known hepatotoxin. Furthermore, two of the four patients undergoing second alloSCT developed VOD, suggesting that this group of patients is also at higher risk. More details focusing on the patients who underwent alloSCT after inotuzumab treatment have recently been published [73].

Recently, a weekly regimen of inotuzumab has been explored as an attempt to reduce toxicity while maintaining antileukemic activity [74]. Patients received inotuzumab at a dose of 0.8 mg/m² IV on day 1, followed by 0.5 mg/m² on days 8 and 15, which cumulatively equal the total dose given on the every 3–4-week schedule ($n = 34$). Response rates on the weekly schedule were comparable to those seen on the single-dose regimen (53% vs. 57%). The weekly schedule also appeared to cause less liver dysfunction, with no occurrences of grade 3 or 4 hyperbilirubinemia (compared to 4% on the single-dose schedule).

T-ALL

For patients with T-ALL, monoclonal antibody therapies are lacking when compared to B-ALL. Alemtuzumab, an antibody that targets CD52, has been used in small studies, but the development has been slow due to very modest activity and a significant side effect profile. In one series, three pediatric patients with relapsed T-ALL were treated with alemtuzumab, and none of them responded [75]. Of note, CD52 is also expressed on normal and malignant B-cells, although the experience using alemtuzumab in B-ALL has also been somewhat disappointing [76].

Recently, genetic profiling of T-ALL has provided some intriguing insight into potential treatment strategies for certain subsets of patients. One subtype of T-ALL has been termed early T-cell precursor (ETP) ALL [77]. Patients have a distinct immunophenotype, in which

the leukemic blasts are negative for CD1a and CD8, negative or weakly positive for CD5, and exhibit concomitant expression of myeloid or stem cell markers (e.g. CD13, CD33, CD34, CD117). Perhaps the most clinically relevant finding of this study was that ETP-ALL is pathophysiologically similar to a myeloid hematopoietic process. The suggestion is that perhaps therapy normally used to treat acute myeloid leukemia may be a rational approach in this disease. The investigators identified mutations in several genes involved in histone regulation, making it reasonable to study the effectiveness of epigenetic therapy (i.e. histone deacetylase inhibitors, hypomethylating agents) in these patients. Finally, patients with ETP-ALL tend to harbor mutations commonly found in acute myeloid leukemia (AML), such as FLT3 or RAS. Testing for these mutations in ETP-ALL will allow researchers to test whether kinase inhibitors that target these lesions are effective.

NOTCH-1 is a receptor tyrosine kinase and transcription factor that is involved in normal T-cell differentiation and maturation [78]. More than half of patients with T-ALL have activating mutations of NOTCH, making it a good candidate for therapeutic targeting. Once the receptor is bound by ligand, gamma secretase cleaves its intracellular domain, which subsequently moves to the nucleus and activates the transcription of target genes. Gamma secretase inhibitors have been developed as a possible mode of blocking this critical step in NOTCH activation. One such compound, MK-0752, was tested at escalating doses in seven patients with relapsed T-ALL [79]. Lack of objective responses and unacceptable gastrointestinal toxicities (severe diarrhea) led to early closure of the clinical trial. As it turns out, NOTCH signaling is important in regulation of the intestinal epithelium, and gamma secretase inhibition leads to accumulation of mucus secreting goblet cells [78]. This toxicity may be obviated by combining gamma secretase inhibitors with corticosteroids [80]. Newer gamma secretase inhibitors under development will likely test this hypothesis clinically.

Conclusions

Improvements in therapy for adult ALL are highly encouraging. Rituximab has been shown to improve survival when combined with conventional chemotherapy. Blinatumomab and inotuzumab have demonstrated marked activity even in multiply refractory patients. The role of monoclonal antibodies and other novel targeted approaches in adult ALL continue to be defined. The majority of these agents are currently being evaluated in the relapsed setting, although the most active agents will likely need to be incorporated into the frontline treatment plan to optimize efficacy. One current example of this approach in elderly patients combines two monoclonal antibodies, rituximab and inotuzumab, with a conventional chemotherapy regimen [81]. Notably, doses of cytotoxic chemotherapy on this protocol are significantly reduced, and anthracyclines are omitted completely, as these agents tend to cause severe toxicity in this patient group. Strategies such as these will continue to be developed and refined with the goal of achieving cure rates that approach those observed in pediatric patients.

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Table I

Targeted therapies for acute lymphoblastic leukemia.

CD19		
SAR3419		Conjugated to a synthetic maytansinoid that is released intracellularly after antigen internalization
Blinatumomab		Bispecific antibody that redirects cytotoxic T-cells to cells that express CD19
CAR-T cells		Patient specific T-cells engineered to attack cells that express CD19
CD20		
Rituximab		When added to conventional chemotherapy, has been shown to improve survival in younger adults
Ofatumumab		Binds to a different epitope than rituximab, which may allow it to overcome rituximab-resistant disease
CD22		
Epratuzumab		Studied as part of combination therapy in adults and children with modest activity
Epratuzumab-SN-38		Antibody conjugated to a topoisomerase I inhibitor to enhance cell killing potential
Inotuzumab ozogamicin		Antibody conjugated to the cytotoxin calicheamicin
CD52		
Alemtuzumab		Antibody that has displayed only little activity in B- and T-cell disease