Title

New insights into the pathophysiology and therapy of adult acute lymphoblastic leukemia.

Journal

Cancer, 121(15)

Authors

Jabbour, Elias

OBrien, Susan

Konopleva, Marina

et al.

Publication Date

2015-08-01

DOI

10.1002/cncr.29383

Peer reviewed

HHS Public Access

Author manuscript

Cancer. Author manuscript; available in PMC 2025 January 13.

Published in final edited form as:

Cancer. 2015 August 01; 121(15): 2517–2528. doi:10.1002/cncr.29383.

New Insights into the Pathophysiology and Therapy of Adult Acute Lymphoblastic Leukemia

Elias Jabbour,

Susan O'Brien,

Marina Konopleva,

Hagop Kantarjian

Department of Leukemia, U.T. M.D. Anderson Cancer Center, Houston, TX

Abstract

Significant advances have been made in the last decade toward a better understanding of the disease pathogenesis and the development of novel therapies that target specific subsets of adult acute lymphoblastic leukemia (ALL). Risk-adapted strategies are transforming the disease treatment and prognosis. With current treatment regimens, long-term survival is achieved in approximately 50% of patients with B-cell ALL, 50%-60% with Philadelphia-chromosome-positive ALL, and around 80% with Burkitt's leukemia. Genomic profiling in ALL identified new prognostic markers, new therapeutic targets, and novel ALL subtypes. These may be amenable to future targeted therapies that can further improve the outcome. The early recognition of early precursor T-ALL, a distinct pathobiological entity of poor prognosis, is essential for the development of an effective clinical management strategy. The role of monoclonal antibodies and cytotoxic T cell therapies continues to be defined. Many of the approaches are currently being evaluated in ALL salvage. Their incorporation into frontline adult ALL therapy, in concomitant or sequential strategies, may increase the cure rates to levels achieved in pediatric ALL, and may reduce the need for prolonged intensive and maintenance chemotherapy.

Keywords

Acute lymphoblastic leukemia; management; outcome

Introduction

Acute lymphoblastic leukemia (ALL) is a hematologic malignancy driven by the proliferation and accumulation of lymphoid progenitor cells in the bone marrow and other tissues. It occurs in a bimodal distribution and an overall age-adjusted incidence of 1.7 per 100,000 persons, affects 4–5 children/100,000, and half that number around the fifth decade of life.[1–3] Roughly 60% of cases are diagnosed in patients younger than age 20. In 2014, an estimated 6000 patients were diagnosed with ALL.[1–3] Although ALL represents only 20% of adult leukemias, it is the most common childhood acute leukemia (80% of cases).

Address Correspondence: Elias Jabbour, Department of Leukemia, The University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd. Box 428. Houston, TX 77030,Phone: 713-7924764; Fax: 713-794-4297;, ejabbour@mdanderson.org.

This makes the management of ALL complex, as patient and leukemic factors have to be considered when designing a therapeutic plan.

ALL is highlighted as a cancer success story for pediatric patients, with cure rates of 80+% reported in recent studies. This was accomplished through optimizing the doses and schedules of the same chemotherapeutic agents used for the previous five decades.[4–5] In adult ALL, the same magnitude of success has not been realized using similar strategies; the cure rate is estimated to be 20 to 40%.[6–7] Adult present with higher risk features at diagnosis, predisposing to chemotherapy resistance and disease relapse after initial achievement of complete remission (CR). Incorporation of targeted agents in adult ALL therapy has improved survival in several subsets.[8–12]

Significant advances have been made in the last decade toward understanding the disease pathogenesis, refinement of prognostic groups, and development of novel therapies that target specific subsets. Risk-adapted therapies are now producing significant improvements in survival. With the current treatment regimens, long-term survival rates are achieved in approximately 80% in Burkitt's leukemia,[8–9] 50% in B-cell ALL,[10] 50%-60% in Philadelphia (Ph)-chromosome-positive ALL,[11–12] and 50–60% in T-cell ALL.[13]

Critical Diagnostic Evaluation

At diagnosis, patients are stratified by a number of factors that help determine prognosis and 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 (e.g. CD20, CD19, CD22). Cytogenetic analysis distinguishes patients whose leukemic cells harbor the Philadelphia chromosome [i.e. t(9;22)] (Ph) or other chromosomal alterations with prognostic relevance [e.g. Burkitt Karyotypes or t(4;11)] (Table 1). Molecular studies uncover gene mutations that may result in aberrant pathway activation and cell survival. ALL genomes have a lower burden of genetic alterations than many solid tumors, with focal deletions being the hallmark of lymphoid leukemia. Using genome-wide gene-expression arrays, investigators identified patients, without BCR-ABL1 fusion protein expressed from the t(9;22)(q34;q11.2) having a gene expression profile similar to BCR-ABL1 ALL.[14–15] This new identity was defined as Ph-like ALL. This so-called BCR-ABL1-like disease had a poor prognosis similar to the historical poor prognosis of Ph-positive ALL prior to the addition of Bcr-Abl tyrosine kinase inhibitors (TKI) to chemotherapy for this ALL subset. The frequency of Ph-like ALL is 10% among children with standard-risk ALL and as high as 25%-30% among young adults with ALL.[16–17] Genetic characterization showed more than 80% of cases had deletions in key transcription factors involved in B-cell development like IKZF1, TCF3, EBF1, PAX5, and VPREB1. Kinase-activating alterations were identified in 90% of patients with Ph-like ALL. Rearrangements involving ABL1, ABL2, CRLF2, CSF1R, EPOR, JAK2, NTRK3, PDGFRB, PTK2B, TSLP, or TYK2 and sequence mutations involving FLT3, IL7R, or SH2B3 were most common. The most common (~50%) are rearrangement of CRLF2, encoding a component of the receptor for TSLP (thymic stromal lymphopoietin), either as a translocation to the immunoglobulin heavy chain enhancer region at 14q32.33 (*IGH-CRLF2*); as a deletion involving the pseudoautosomal region 1 (PAR1) of Xp22.3/

Yp11.3 adjacent to *CRLF2* resulting in the expression of a *P2RY8-CRLF2* fusion transcript; or as CRLF2 F232C mutation.[18–23] These lesions result in overexpression of *CRLF2* mRNA and protein. *CRLF2* rearrangements activate downstream signaling through JAK kinases and in approximately half of the cases have activating mutations in *JAK1* or *JAK2*. Ectopic expression of ABL1, ABL2, CSF1R, JAK2, and PDGFRB fusions resulted in cytokine-independent proliferation and activation of phosphorylated STAT5 in murine bone marrow B cells. Cell lines and human leukemic cells expressing ABL1, ABL2, CSF1R, and PDGFRB fusions were sensitive *in vitro* and in the *in vivo* human xenograft models to ABL-class tyrosine kinase inhibitors (e.g., dasatinib); those with EPOR, IL-7R, and JAK2 rearrangements (mutations and fusions) were sensitive to JAK kinase inhibitors (e.g., ruxolitinib); and those with ETV6-NTRK3 fusion were sensitive to ALK kinase inhibitors (e.g., crizotinib).[16] Furthermore, Roberts an colleagues treated 12 patients with refractory Ph-like ALL with tyrosine kinase inhibitors.[16] Among the 12 patients who began receiving tyrosine kinase inhibitor therapy, 11 with available follow-up data had rapid and sustained responses: 3 of them with EBF1-PDGFRB fusion who responded to ABL tyrosine kinase inhibitor (e.g., imatinib).[16] Therefore, the genomic profiling in ALL identified new prognostic markers (e.g. IKZF1), new therapeutic targets (e.g. JAK), and novel ALL subtypes (Table 2). These may be amenable to future targeted therapies that can improve the adverse prognosis of BCR-ABL1- like ALL.[17] In addition, the genetic basis of hypodiploid ALL, a subtype of ALL characterized by aneuploidy and poor outcome, was recently deciphered.[24] using genome profiling, Holmfeldt and colleagues identified two subtypes that differ in the severity of aneuploidy, transcriptional profiles and submicroscopic genetic alterations. Near-haploid ALL with 24–31 chromosomes harbor alterations targeting receptor tyrosine kinase signaling and Ras signaling (71%) and the lymphoid transcription factor gene IKZF3 (13%). In contrast, low-hypodiploid ALL with 32–39 chromosomes are characterized by alterations in TP53 (91%) that are commonly present in nontumor cells, IKZF2 (53%) and RB1 (41%). Similar findings of high frequency of TP53 mutations (93%) in patients with low hypodiploid karyotype were reported by Muhlbacher and colleagues with a median survival of 18.5 months.[25] Both near-haploid and low-hypodiploid leukemic cells show activation of Ras-signaling and phosphoinositide 3-kinase-signaling pathways and are sensitive to PI3K inhibitors.[24] Thus, PI3K inhibitors should be explored as a new therapeutic strategy for this aggressive form of leukemia.

Mature B-cell ALL

Outcome for mature B-cell ALL has improved substantially with use of short-term dose-intensive treatment programs. Complete remission rates now exceed 80%, with 2-year disease-free survival (DFS) rates of 60% to 80%. Relapses are rare after the first year in remission. Intensive early prophylactic intrathecal therapy, in addition to intensive systemic administration of cytarabine and methotrexate, reduces the CNS relapse rate.[9]

The addition of rituximab to chemotherapy has improved the cure rates in mature B-cell ALL. Three different studies have reported a significant improvement in the survival rates from 51% to 78% after the addition of rituximab.[8–9, 26]

To further reduce early morbidity and mortality, a pilot study investigated dose adjusted EPOCH in combination with rituximab in 30 patients (median age 33 years; age >40 years, 40%) diagnosed with Burkitt lymphoma. The treatment was safe and highly effective. The progression-free and overall survival rates were 95–100% and 90–100%, respectively. Of note, the majority of patients (90%) were of low- and intermediate risk disease:[27] only 13% had marrow involvement and 3% had central nervous system (CNS) involvement, both known adverse factors. Ongoing trials are assessing this regimen in mature B-cell ALL.

CD20 positive pre-B ALL

The addition of rituximab to the hyperCVAD regimen in newly diagnosed patients with Philadelphia-negative, CD20-positive ALL was evaluated, adding 2 doses of rituximab with each of the first four cycles of intensive chemotherapy (total 8 doses of rituximab).[9] Rituximab was also incorporated into early and late intensification cycles (months 6 and 18 of maintenance therapy). Among patients < 60 years old, the addition of rituximab improved CR duration (70% versus 38%; P < .001%) and 3-year survival rates (75% versus 47%; P = 0.003). The German Multicenter Study Group for ALL (GMALL) also reported an improvement in the 5-year remission duration and survival rates with the addition of rituximab to standard induction and consolidation chemotherapy in patients < 55 years old.[28]

Ofatumumab is a more potent second generation anti-CD20 monoclonal antibody that binds to a site different than rituximab.[29] In a phase II study in de-novo pre-B CD20-positive ALL, the combination of HCVAD with ofatumumab was effective.[30] Ofatumumab was given as 2 grams twice per course in the first 4 courses. Among the initial 30 patients treated, the rates of CR and minimal residual disease (MRD; by six color multiparameter flow) negativity were 96% and 93%, respectively. With a median follow-up of 16 months, the one-year progression-free and overall survival rates were 85% and 88%, respectively.[30]

Philadelphia chromosome (Ph)-positive ALL

Patients with Ph-positive ALL had traditionally a very poor outcome with anti-ALL chemotherapy particularly if they did not undergo allogeneic stem cell transplantation (allo-SCT) in first CR.[31] The incorporation of BCR-ABL1 tyrosine kinase inhibitors (TKIs) to chemotherapy has improved outcome significantly. The best results are shown with the TKIs incorporated early, daily, and continuously with chemotherapy with chemotherapy.[10, 32–35] The TKIs should be started immediately upon recognition of Ph-positive disease, and prolonged continuous exposure to TKIs is superior to pulsed or intermittent administration.[10, 35–36]

Second generation TKIs initially developed for patients who are intolerant of or failing imatinib are more potent than imatinib.[37–38] Dasatinib also inhibits SRC kinases, which have been implicated in the pathophysiology of Ph-positive ALL.[39] Ravandi and colleagues administered dasatinib at 100 mg daily for 14 days with induction chemotherapy then at 70 mg continuously throughout the consolidation cycles, and at 100 mg daily on a continuous basis during maintenance therapy.[11] Among 72 patients treated, the CR,

complete cytogenetic response (CCyR), and the complete molecular response (CMR) rates were 94%, 96% and 65%, respectively. Twenty-two patients underwent allo-SCT (12 in CR1 and 10 in CR2). The 3-year disease-free and survival rates were 49% and 61%, respectively. There was no difference in outcome between patients in CR1 who did and did not undergo allo-SCT.

Other studies combining dasatinib or nilotinib with intensive or or low-intensity chemotherapy are also showing encouraging results.[40–43] In the GRAAPH-2005 study, 265 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.[40] Patients received similar consolidation, and the ultimate plan was for all patients to receive an allo-SCT or an autologous SCT (auto-SCT). The CR rate after induction was higher in the low intensity group, mainly due to excess induction related mortality in hyperCVAD group (7% vs. < 1%; $p = 0.01$). An equal number of patients in each group proceeded to auto-SCT and allo-SCT. At 3 years, survival 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 .[41] Seventy-one patients treated received induction with dasatinib 140 mg once daily combined with vincristine and dexamethasone. Consolidation therapy included dasatinib 100 mg daily combined with methotrexate and asparaginase alternating with cytarabine. The CR rate was 94%. Five patients subsequently underwent allo-SCT. The estimated 3-year survival rate was 45%. Among 29 patients who had ALL relapse, a T315I mutation was noted in 63%. Similar results were recently reported using nilotinib with low intensity chemotherapy (EWALL-Ph-02)[42] and dasatinib in combination with steroids (LAL 1509).[43]

Many patients with Ph-positive ALL relapse with a T315I clone which is resistant to imatinib and second-generation TKIs.[41, 43] This underscores the fact that resistant disease can still emerge under treatment with second-generation TKIs, and the possible value of ponatinib in this setting. Ponatinib is a third generation more potent BCR-ABL1 TKI which also suppresses the T315I clones.[44–45] Thirty-nine patients with newly diagnosed Philadelphia-positive ALL were treated with HCVAD and ponatinib 45 mg daily for the 14 days during induction, then continuously thereafter with possible dose descalation to 30 mg and 15 mg daily once a CCyR and CMR were obtained respectively. The CR, CCyR and CMR rates were 100%, 100%, and 74%, respectively. Grade ≥ 3 toxicity included infections during induction (49%), increased LFT's (35%), thrombotic events (8%), myocardial infarction (8%), skin rash (11%), and pancreatitis (16%). Two potential related deaths from myocardial infarction were observed. This led to adjust the ponatinib dose, where it is currently administered at 45 mg daily for 14 days during induction, then 30 mg daily continuously till the achievement of complete molecular remission, then 15 mg daily infinitely thereafter. With a median follow-up of 20 months, the 1-year progression-free and overall survival rates were 97% and 87%, respectively.[46]

While allo-SCT has improved the outcome of patients with Ph-positive ALL, there is now some debate as to who should be referred for allo-SCT in first CR. Ravandi and colleagues evaluated the predictive value of MRD assessment by RQ-PCR and by multiparameter flow cytometry (FCM) in patients with Ph-positive ALL treated with combination chemotherapy and TKIs, but without an allo-SCT.[47] Patients achieving MMR at 3, 6, 9, and 12 months had a better survival; the 3-year survival rates were 67% and 47% (p=0.02), 67% and 50% (p=0.04), 67% and 49% (p=0.05), and 80% and 48% (p=0.01), in patients with and without MMR, respectively. Negative FCM at 3 and 12 months was associated with improved survival (P = .04 and .001) as well; the 3-year survival rates were 70% and 25% (p=0.04) 80% and 20% (p=0.001) in patients with negative and positive FCM, respectively. Therefore, MRD monitoring by RQ-PCR and FCM may identify patients in first CR in whom further consolidation with allo-SCT may not be needed.[47]

T-cell ALL

Therapy of patients with T-cell ALL is similar to those with B-cell ALL. Nelarabine is a deoxyguanosine analog that selectively accumulates in T-cells, thus making it an intriguing compound for the management of T-ALL.[48] The drug is currently approved as a third-line option in pediatric and adult patients with relapsed ALL,[49] and may be of optimal use in the frontline setting. We evaluated nelarabine in combination with the hyperCVAD regimen in 48 patients (median age 38 years) with newly diagnosed T-ALL or T-cell lymphoblastic lymphoma (LL) (n = 36).[50] Nelarabine was given either after or during consolidation chemotherapy at a dose of 650 mg/m^2 IV daily for 5 days. The CR rate was 93%. With a median follow-up of 41 months, the 5-year survival rate was 66%. These rates were 38% and 70% for patients with early T-cell precursor (ETP) and mature T-ALL, respectively.

ETP-ALL is a distinct pathobiological entity that confers a poor prognosis with use of standard intensive chemotherapy. ETP-ALL is characterized by distinct cell-surface features that readily enable diagnosis: absence of CD1a, surface CD3, and CD8 expression, weak CD5 expression, and expression of one or more myeloid-associated or stem-cell associated markers.[51] Furthermore, cases of ETP-ALL showed increased genomic instability, in terms of number and size of gene lesions, compared with those with typical T-ALL. Patients with ETP-ALL have high rates of remission failure and relapse (72% at 10 years versus 10% at 10 years for patients with typical T-ALL).[52] Its early recognition, using gene expression and immunophenotypic criteria, is essential for the development of an effective clinical management strategy. Anti-ALL therapy followed by allo-SCT should be considered in first remission in patients with ETP-ALL. In addition to mutations in genes known to be involved in leukemogenesis, more than 60% of adult patients with ETP-ALL harbor at least a single genetic lesion in DNMT3A, FLT3, or NOTCH1 that may be sensitive to targeted therapies.[52] ETP ALL are characterized by activating mutations in genes regulating cytokine receptor and RAS signalling (67%), inactivating lesions disrupting haematopoietic development (58%) and histone-modifying genes (48%).[53] The mutational spectrum is similar to myeloid malignancies, and moreover, the global transcriptional profile of ETP ALL is similar to that of normal and myeloid leukaemia haematopoietic stem cells.[53] Therefore the addition of myeloid-directed therapies might improve the poor outcome of ETP ALL.

Adolescent and Young Adults

Recent data suggested that adults with ALL may benefit from pediatric-inspired chemotherapy regimens (higher cumulative exposure to non-myelossuppressive agents like asparaginase, steroids, vincristine) compared with historical adult regimens which had deviated significantly from the spirit of pediatric regimens.[54–56]

In a retrospective review analyzing adolescent and young adult patients (AYA; ages 16–20) over a 13-year period enrolled on adult or pediatric regimens, outcomes were superior with pediatric studies.[54] This included a statistically significant difference in the 7-year survival rates between the two groups (67% vs. 46%; $p < 0.001$). Notably, there was a significant difference in baseline age between the two groups, which might explain such of the difference: 85% of patients in the pediatric protocols group were 16–17 years old, compared with 20% in the adult protocols. When only considering 16–17 year olds, the event-free survival (EFS) was similar with adult versus pediatric regimes.

Stock et al recently reported the results of US Intergroup study for 318 AYA (16 to 36 years; median age 25 years) treated with a pediatric-inspired regimen. Of note 14% of patients enrolled were younger than 20 years. The 2-year event-free and overall survival rates were 66% and 78%, respectively.[55] The estimated 5-year rates were 49% and 66%, respectively.

The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) tested the concept in patients up to the age of 60 years.[56] Among 225 patients treated, the CR rate was 93%. Outcomes were compared to a historical control group treated with an adult (LALA) regimen. The pediatric-inspired regimen resulted in a significantly improved survival (66% vs. 44%; $p < 0.001$). However, in patients 40 to 60 years old, the cumulative incidence of chemotherapy-related death was 23%, essentially negating any incremental benefit offered by enhanced antileukemic activity. Intensifying the chemotherapy regimen to “pediatric strength” may have a finite capability to increase the cure rate in adult ALL, because eventually a toxicity threshold will be crossed.

Patel and colleagues reported the UKALL14 experience using peg-asparaginase at the dose of 1000 units/m^2 on D4 and D18 during induction in 91 adults with a median age of 47 years (range, 25–65). The CR rate was 66%, the induction mortality 20% and the hepatotoxicity rate 56%. These findings prompted the investigators to omit peg-asparaginase in patients 40 years and older.[57]

At MD Anderson Cancer Center, 85 AYA (median age 21 years; range, 12–40 years) were prospectively treated with the Augmented Berlin-Frankfurt-Muenster (ABFM) pediatric inspired regimen.[58] The CR and minimal residual disease negativity rates were 94% and 69%, respectively. Serious adverse events included severe asparaginase allergies in 20%, pancreatitis in 11%, avascular necrosis in 11%, thrombosis in 21%, and liver dysfunction in 33% to 36%. The 5-year CR duration rate was 58% and the 5-year survival rate 62%. Among patients ≥ 21 years, the 5-year survival rate was 58%. The results obtained with the ABFM regimen were comparable with those achieved with HCVAD +/− rituximab. The overall 3-year survival rates were 72% and 71%, respectively. The pediatric inspired regimen

was more toxic (pancreatitis, liver dysfunction, thrombosis, osteonecrosis), and worse than the combination of HCVAD with anti-CD20 therapies in patients 25 years and older.

In summary, while the modifications implemented in the common adult ALL regimens have shifted away from the backbone ALL therapies applied in pediatric leukemias, the hyper-CVAD regimen, which kept such principles but eliminated or reduced asparaginase exposure, showed similar CR, remission duration and survival outcomes compared with the pediatric-inspired regimen in similar patient populations.

Elderly ALL

Elderly patients with ALL (age greater than 60 years) may benefit from a more targeted low-intensity anti-ALL regimen. Older patients are predisposed to severe toxicity from conventional chemotherapy, which is associated with high mortality rate (30–35%) during consolidation-maintenance in CR.[59] The German Multicentre Study Group for Adult ALL (GMALL) reported CR rate of 76%, early death rate of 14%, mortality in CR of 6%, and survival rates of 23% at 5 years in 268 elderly patients treated with less intensive induction and consolidation regimen.[60] Twenty-six older patients (median age of 67 years; range, 60 to 79) with newly diagnosed ALL were treated in a phase II study with inotuzumab and low-intensity hyperCVD therapy.[61] The regimen eliminated doxorubicin in induction, used cyclophosphamide and steroids at 50% of the dose of previous regimens, and reduced methotrexate to 250 mg/m^2 on Day 1 and cytarabine to 0.5 mg/m^2 × 4 (Days 2 and 3) of even courses. Inotuzumab, a targeted CD22 monoclonal antibody bound to calicheamicin (a chemotoxin), was added at a dose of 1.3–1.8 mg/m^2 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 is being evaluated in adult patients with relapsed/refractory (R/R) disease as well.

Role of allogeneic stem cell transplantation

Patients with high risk features at diagnosis are typically recommended to undergo allo-SCT 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 × 10^9/L for B-ALL, or 100 × 10^9/L for T-ALL) and hypodiploidy. A large study found that patients with standard risk ALL (i.e. the absence of high risk features) benefited from allo-SCT in first CR, while those with high-risk disease did not benefit.[62] This has caused considerable debate regarding which patients should be referred for transplantation. 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. The German

studies update suggest equal benefits from modern intensive ALL regimens compared to allo-SCT.[26]

Perhaps the most important prognostic marker in ALL is the presence or absence of minimal residual disease (MRD).[63–70] Bassan and colleagues used MRD status at various time points after CR had been attained to guide treatment in adult patients with ALL.[64] 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 allo-SCT 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).

The use of gene expression and immunophenotypic techniques are crucial in early identifying patients with poor prognosis (e.g. ETP-ALL and Ph-like ALL) in whom allo-SCT should be considered in first CR.[14–15, 51]

These data suggest that the decision to perform allo-SCT 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 allo-SCT 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.

Minimal Residual Disease

Persistence or reappearance of MRD after induction chemotherapy is the most important adverse prognostic factor in patients with ALL and identifies chemo-refractory disease.[63–70] More than 90% of patients who have persistent MRD after chemotherapy experience a clinical relapse, despite continued chemotherapy with a median time to relapse of 4–5 months.[70] A multivariate analysis of a series of 326 adolescent and adult patients with high-risk Philadelphia chromosome-negative ALL treated in the PETHEMA ALL-AR-03 trial showed poor MRD clearance defined as levels $\geq 1 \times 10^{-3}$ after induction and $\geq 5 \times 10^{-4}$ after early consolidation, by FCM as the only prognostic factor for disease-free and overall survival.[71]

Gokbuget and colleagues investigated the role of allo-SCT in 120 patients with positive MRD after first consolidation (week 16). The median time from CR to allo-SCT was 7 months.[70] The 5-year continuous CR rate was significantly higher for patients with positive MRD and allo-SCT in first CR than for those without allo-SCT in first CR (66% ± 7% vs 12% ± 5%; P < .0001). Results were similar for disease-free survival.[70] Blinatumomab, a bispecific T-cell engaging (BiTE) antibody 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.[72] In the first study, 21 patients in hematologic and morphologic CR with persistent or reappearing MRD during consolidation chemotherapy were treated with blinatumomab 15 mcg/m^2/day as a continuous infusion for 28 days every 6 weeks, for

up to 4 total cycles or proceed to allo-SCT if a donor was available.[73] MRD conversion after one cycle was noted 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%.[74] Nine patients underwent allo-SCT, but interestingly, non-transplanted patients had similar favorable outcome compared to the transplant group. In a confirmatory open-label multicenter phase II trial in 116 patients in morphologic CR with positive MRD positive, the overall rate of conversion to the MRD negativity was 80% (78% occurring after one cycle of treatment).[75]

Salvage Therapies with Monoclonal Antibodies

Despite an exceptionally high rate of initial CR, many adults with ALL will relapse. Current strategies to induce a second remission translating into long-term survival are lacking. Cytotoxic chemotherapy results in modest CR rates of 30–40% in first salvage and 10–20% in later salvages. Few patients can be bridged to allo-SCT, 5–10% in some studies but as high as 30–40% in the German trials.[76–78] This bridging to allo-SCT offers a chance of long term remissions and cures (<20–30%).

One of the most exciting groups of compounds under investigation in relapsed refractory ALL are monoclonal antibodies targeting CD19 and CD22. Of these antibodies, blinatumomab and inotuzumab ozogamicin are in the most advanced investigational phases (Table 3). Blinatumomab was granted FDA approval for the treatment of R/R ALL in December 2014.

Blinatumomab

Blinatumomab was first assessed in patients with positive MRD and subsequently studied in patients with relapsed/refractory (R/R) ALL.[79–80] Three dose levels were explored, all involving blinatumomab administration as a continuous infusion for 28 days every 6 weeks. In the pivotal trial, 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.[79] 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 the first cycle. The median response duration and overall survival were 9 and 6 months, respectively.[80]

The toxicity profile of blinatumomab is acceptable, consisting of fever, chills, and hypogammaglobulinemia. Tremor, headache, other mental status changes (e.g., confusion), and occasional seizures (2%) have been reported. Fever, chills, and other constitutional symptoms are due to a cytokine release syndrome that occurs shortly after the start of therapy, and are reduced with the use of steroids. Serious adverse events are uncommon, but seizures have been observed in both the MRD and active disease settings. Corticosteroids before the first dose and prior to dose escalation ameliorate some toxicities.

Blinatumomab is currently being assessed in a phase III trial in patients with ALL in first or second relapse randomized to either blinatumomab or an investigator’s choice chemotherapy

regimen, in a phase II study in patients with relapsed Ph-positive ALL, and in the frontline setting in MRD-positive ALL.

Inotuzumab ozogamicin

The immunoconjugate directed at CD22 furthest along in development is inotuzumab ozogamicin. The antibody is linked to calicheamicin, a potent cytotoxic compound that induces double-strand DNA breaks.[81] Initial studies in patients with lymphoma established an MTD of 1.8 mg/m^2 IV given every 3 to 4 weeks, with reversible thrombocytopenia emerging as a frequent adverse effect.[82] This led to a single institution phase II study in patients with relapsed-refractory ALL,[83] using inotuzumab at a starting dose of 1.3 mg/m^2 IV every 3 to 4 weeks for the first three patients; later patients received 1.8 mg/m^2. Forty-nine patients were treated, 73% of whom received inotuzumab for ALL second salvage or later. The ORR was 57%, and the median survival was 5.1 months. Nearly half of the patients treated with inotuzumab were able to proceed to allo-SCT (n = 22), including four patients who were receiving a second allo-SCT. Survival was similar whether patients underwent subsequent allo-SCT 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 allo-SCT developed VOD, suggesting this group to be also at high risk for VOD.[84]

To optimize the benefit:risk of inotuzumab, a weekly dosing regimen was evaluated based on preclinical studies indicating that toxicity might be minimized and efficacy maintained.[85] Inotuzumab was given at 0.8 mg/m^2 on Day 1, and 0.5 mg/m^2 on Days 8 and 15, every 3–4 weeks. This is the same cumulative dose per course compared with single infusion inotuzumab every 3–4 weeks. With the weekly regimen, the 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 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 allo-SCT (7% versus 23%). Patients receiving inotuzumab in second salvage 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.[86]

In a second phase II study, 35 patients with Philadelphia-negative in second or later salvage ALL received weekly inotuzumab (1.8 mg/m^2 per cycle).[87] The CR and CR without count recovery rates were 66% (23/35); 18 of 23 patients (78%) in remission achieved MRD negativity. VOD occurred in 3 patients, 2 post allo-SCT. The median overall survival was 7.4 months.

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

Chimeric Antigen Receptor T-cells (CAR T-cells) therapies

Harnessing the patient's immune system to eliminate malignant cells has been an area of oncologic research for decades. Chimeric antigen receptor-modified T-cells have emerged as an effective approach for patients with lymphoid malignancies.[88–89] Autologous T-cells are engineered to express a receptor directed at CD19 which mediates cytotoxicity. These cells have been noted to expand and persist in vivo: this mechanism may confer response durability.

In a pilot study, 30 patients (25 children, 5 adults) with active ALL were treated with lymphodepleting chemotherapy followed by CTL019 infusion.[90] Twenty-seven patients (90%) achieved CR. The 6-months event-free and overall survival rates were 63% and 78%, respectively. All responding patients developed some degree of delayed cytokine release syndrome (CRS) and eight (27%) required anti-CSR therapy (Table 4).

Lee and colleagues recently reported the results of an initial phase I dose-escalation trial in 21 children and young adults with relapsed-refractory ALL who received CAR T-cells post fludarabine and cyclophosphamide.[91] Fourteen of the 21 evaluable ALL patients (70%) achieved CR, 12 of them (60%) achieving MRD-negativity. Overall survival at a median follow-up of 10 months was 52%. All toxicities were fully reversible, with the most severe being grade 4 CSR that occurred in three (14%) of 21 patients (Table 4).

Davila and colleagues treated 24 adult patients with relapsed-refractory ALL received CAR T-cells following conditioning chemotherapy.[92] Twelve of the 22 evaluable patients (54%) had active disease before T cell infusion responded. Twenty of the 22 patients (91%) achieved a CR. In addition, 80% achieved a MRD-negative CR. Nine patients developed CRS that resolved post steroids or trocilizumab, essentially observed in patients with active disease at the time of the T cell infusion (Table 4).

Turtle and colleagues treated 9 patients with R/R ALL.[93] Five of the seven evaluable ALL patients achieved CR. Severe CRS was observed in all patients with high tumor burden. Continued research on the optimal clinical use of this highly innovative strategy will be important.

Conclusions

Improvements in the therapy of adult ALL are highly encouraging. Targeted therapies have 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, the chimeric CAR-T cell therapies, and other novel targeted approaches in adult ALL continue to be defined. The majority of these agents are currently being evaluated in the salvage setting, although the most active agents will likely need to be incorporated into the frontline treatment plan to optimize efficacy and decrease toxicities. 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.

References

1. Society AC. American Cancer Society. Cancer Facts and Figures 2014. 2014.
2. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. CA. Cancer J. Clin. 62 (1) 10–29.
3. Inaba H, Greaves M, Mullighan CG. Acute lymphoblastic leukaemia. Lancet. 2013; 381 (9881) 1943–55. [PubMed: 23523389]
4. Pui CH, Campana D, Pei D, et al. Treating childhood leukemia without cranial irradiation. N Engl J Med. 2009; 360: 2730–41. [PubMed: 19553647]
5. Pui CH, Mullighan CG, Evans WE, Relling MV. Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? Blood. 2012; 120: 1165–74. [PubMed: 22730540]
6. Kantarjian HM, Thomas D, O'Brien S, et al. Long-term follow-up results of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD), a dose-intensive regimen, in adult acute lymphocytic leukemia. Cancer. 2004; 101: 2788–2801. [PubMed: 15481055]
7. Sive JI, Buck G, Fielding A, et al. Outcomes in older adults with acute lymphoblastic leukaemia (ALL): results from the international MRC UKALL XII/ECOG 2993 trial. Br J Haematol. 2012; 157 (4) 463–471. [PubMed: 22409379]
8. Hoelzer D, Walewski J, Döhner H, et al. Improved outcome of adult Burkitt lymphoma/leukemia with rituximab and chemotherapy: report of a large prospective multicenter trial. Blood. 2014; 124 (26) 3870–3879. [PubMed: 25359988]
9. Thomas DA, Faderl S, O'Brien S, et al. Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. Cancer. 2006; 106 (7) 1569–1580. [PubMed: 16502413]
10. Thomas DA, O'Brien S, Faderl S, et al. Chemoimmunotherapy with a modified hyper-CVAD and rituximab regimen improves outcome in de novo Philadelphia chromosome-negative precursor B-lineage acute lymphoblastic leukemia. J Clin Oncol. 2010; 28 (24) 3880–3889. [PubMed: 20660823]
11. Fielding AK, Rowe JM, Buck G, et al. UKALLXII/ECOG2993: addition of imatinib to a standard treatment regimen enhances long-term outcomes in Philadelphia positive acute lymphoblastic leukemia. Blood. 2014; 123 (6) 843–850. [PubMed: 24277073]
12. Ravandi F, O'Brien S, Thomas D, et al. First report of phase II study of dasatinib with hyper-CVAD for the frontline treatment of patients with Philadelphia chromosome-positive (Ph+) acute lymphoblastic leukemia. Blood. 2010; 116: 2070–2077. [PubMed: 20466853]
13. Jain P, Kantarjian H, Ravandi F, et al. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. Leukemia. 2014; 28 (4) 973–975. [PubMed: 24157581]
14. Mullighan CG, Su X, Zhang J, et al. Deletion of IKZF1 and prognosis in acute lymphoblastic leukemia. N Engl J Med. 2009; 360 (5) 470–480. [PubMed: 19129520]
15. Den Boer ML, van Slegtenhorst M, De Menezes RX, et al. A subtype of childhood acute lymphoblastic leukaemia with poor treatment outcome: a genome-wide classification study. Lancet Oncol. 2009; 10 (2) 125–134. [PubMed: 19138562]
16. Roberts KG, Li Y, Payne-Turner D, et al. Targetable kinase-activating lesions in Ph-like acute lymphoblastic leukemia. N Engl J Med. 2014; 371 (11) 1005–1015. [PubMed: 25207766]
17. Harvey RC, Mullighan CG, Chen IM, et al. Rearrangement of CRLF2 is associated with mutation of JAK kinases, alteration of IKZF1, Hispanic/Latino ethnicity, and a poor outcome in pediatric B-progenitor acute lymphoblastic leukemia. Blood. 2010; 115 (26) 5312–5321. [PubMed: 20139093]
18. Mullighan CG, Collins-Underwood JR, Phillips LA, et al. Rearrangement of CRLF2 in B-progenitor- and Down syndrome-associated acute lymphoblastic leukemia. Nat Genet. 2009; 41 (11) 1243–1246. [PubMed: 19838194]
19. Russell LJ, Capasso M, Vater I, et al. Deregulated expression of cytokine receptor gene, CRLF2, is involved in lymphoid transformation in B-cell precursor acute lymphoblastic leukemia. Blood. 2009; 114 (13) 2688–2698. [PubMed: 19641190]
20. Roberts KG, Morin RD, Zhang J, et al. Genetic alterations activating kinase and cytokine receptor signaling in high-risk acute lymphoblastic leukemia. Cancer Cell. 2012; 22 (2) 153–166. [PubMed: 22897847]

21. Hertzberg L, Vendramini E, Ganmore I, et al. Down syndrome acute lymphoblastic leukemia, a highly heterogeneous disease in which aberrant expression of CRLF2 is associated with mutated JAK2: a report from the International BFM Study Group. Blood. 2010; 115 (5) 1006–1017. [PubMed: 19965641]
22. Yoda A, Yoda Y, Chiaretti S, et al. Functional screening identifies CRLF2 in precursor B-cell acute lymphoblastic leukemia. Proc Natl Acad Sci U S A. 2010; 107 (1) 252–257. [PubMed: 20018760]
23. Roberts KG, Pei D, Campana D, et al. Outcomes of children with BCR-ABL1-like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. J Clin Oncol. 2014; 32 (27) 3012–20. [PubMed: 25049327]
24. Holmfeldt L, Wei L, Diaz-Flores E. The genomic landscape of hypodiploid acute lymphoblastic leukemia. Nat Genet. 2013; 45 (3) 242–252. [PubMed: 23334668]
25. Mühlbacher V, Zenger M, Schnittger S, et al. Acute lymphoblastic leukemia with low hypodiploid/near triploid karyotype is a specific clinical entity and exhibits a very high TP53 mutation frequency of 93%. Genes Chromosomes Cancer. 2014; 53 (6) 524–536. [PubMed: 24619868]
26. Rizzieri DA, Johnson JL, Byrd JC, et al. Improved efficacy using rituximab and brief duration, high intensity chemotherapy with filgrastim support for Burkitt or aggressive lymphomas: cancer and Leukemia Group B study 10 002. Br J Haematol. 2014; 165 (1) 102–11. [PubMed: 24428673]
27. Dunleavy K, Pittaluga S, Shovlin M, et al. Low-intensity therapy in adults with Burkitt's lymphoma. N Engl J Med. 2013; 369 (20) 1915–25. [PubMed: 24224624]
28. Hoelzer D, Gökbuget N. Chemoimmunotherapy in acute lymphoblastic leukemia. Blood Rev. 2012; 26 (1) 25–32. [PubMed: 21958552]
29. Arzerra (ofatumumab) Package Insert. Research Triangle Park, NC: GlaxoSmithKline; September, 2011
30. Jabbour E, Kantarjian H, Thomas D, et al. Phase II study of the hyper-CVAD regimen in combination with ofatumumab as frontline therapy for adults with CD-20 positive acute lymphoblastic leukemia. J Clin Oncol. 2014.
31. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia---results of the prospective multicenter LALA-94 trial. Blood. 2002; 100: 2357–66. [PubMed: 12239143]
32. Thomas DA, O'Brien SM, Faderl S, et al. Long-term outcome after hyper-CVA and imatinib (IM) for de novo or minimally treated Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph-ALL). J Clin Oncol. 2010; 28: 15s.
33. Tanguy-Schmidt A, Rousselot P, Chalandon Y, et al. Long-term follow up of the imatinib GRAAPH-2003 study in newly diagnosed patients with de novo Philadelphia chromosome-positive acute lymphoblastic leukemia: a GRAALL study. Biol Blood Marrow Transplant. 2013; 19: 150–155. [PubMed: 22960387]
34. Bassan R, Rossi G, Pogliani EM, et al. Chemotherapy-phased imatinib pulses improve long-term outcome of adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia: Northern Italy Leukemia Group protocol 09/00. J Clin Oncol. 2010; 28: 3644–3652. [PubMed: 20606084]
35. Pfeifer H, Goekbuget N, Volp C, et al. Long-term outcome of 335 patients receiving different schedules of imatinib and chemotherapy as front-line treatment for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood (ASH Annual Meeting Abstracts). 2010; 116
36. Wassmann B, Pfeifer H, Goekbuget N, et al. Alternating versus concurrent schedules of imatinib and chemotherapy as front-line therapy for Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL). Blood. 2006; 108 (5) 1469–1477. [PubMed: 16638934]
37. Kantarjian HM, Shah NP, Cortes JE, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012; 119: 1123–1129. [PubMed: 22160483]
38. Saglio G, Kim D-W, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010; 362: 2251–2259. [PubMed: 20525993]
39. Hu Y, Liu Y, Pelletier S, et al. Requirement of SRC kinases Lyn, Hck and Fgr for BCR-ABL1-induced B-lymphoblastic leukemia but not chronic myeloid leukemia. Nat Genet. 2004; 36: 453–461. [PubMed: 15098032]

40. Chalandon Y, Thomas X, Hayette S, et al. Is less chemotherapy detrimental in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia treated with high-dose imatinib? Results of the prospective randomized GRAAPH-2005 study. Blood. 2012; 120 (Suppl. 1)
41. Rousselot P, Coude MM, Huguet F, et al. Dasatinib and low intensity chemotherapy for first-line treatment in patients with de novo Philadelphia positive ALL aged 55 and over: final results of the EWALL-Ph-01 study. Blood. 2012; 120 (Suppl. 1)
42. Ottman OG, Pfeifer H, Cayuela JM, et al. Nilotinib (Tasigna) and chemotherapy for first-line treatment in elderly patients with de novo Philadelphia chromosome/BCR-ABL1 positive acute lymphoblastic leukemia (ALL): a trial of the European working group for adult ALL (EWALL-PH-02). Blood. 2014; 124
43. Chiaretti S, Vitale A, Elia L, et al. First results of the multicenter total therapy GIMEMA LAL 1509 protocol for de novo adult Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) patients. Blood. 2014; 124
44. O'Hare T, Shakespeare WC, Zhu X, et al. AP24534, a pan- BCR-ABL inhibitor for chronic myeloid leukemia, potently inhibits the T315I mutant and overcomes mutation-based resistance. Cancer Cell. 2009; 16: 401–412. [PubMed: 19878872]
45. Cortes JE, Kantarjian H, Shah NP, et al. Ponatinib in refractory Philadelphia chromosome-positive leukemias. N Engl J Med. 2012; 367: 2075–2088. [PubMed: 23190221]
46. O'Brien S, Jabbour E, Thomas D, et al. Phase II study of combination of hyperCVAD with ponatinib in frontline therapy of patients with Philadelphia chromosome positive acute lymphoblastic leukemia. J Clin Oncol. 2014.
47. Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. Blood. 2013; Aug 15; 122 (7) 1214–21. [PubMed: 23836561]
48. DeAngelo DJ. Nelarabine for the treatment of patients with relapsed or refractory T-cell acute lymphoblastic leukemia or lymphoblastic lymphoma. Hematol Oncol Clin North Am. 2009; 23: 1121–1135. [PubMed: 19825456]
49. Arranon (nelarabine) package insert. Research Triangle Park, NC: GlaxoSmithKline; December, 2011
50. Jain P, Kantarjian HM, Ravandi F, et al. The combination of hyper-CVAD plus nelarabine as frontline therapy in adult T-cell acute lymphoblastic leukemia and T-lymphoblastic lymphoma: MD Anderson Cancer Center experience. Leukemia. 2014; 28 (4) 973–5. [PubMed: 24157581]
51. Coustan-Smith E, Mullighan CG, Onciu M, et al. Early T-cell precursor leukaemia: a subtype of very high-risk acute lymphoblastic leukaemia. Lancet Oncol. 2009; 10 (2) 147–156. [PubMed: 19147408]
52. Neumann M, Heesch S, Schlee C, et al. Whole-exome sequencing in adult ETP-ALL reveals a high rate of DNMT3A mutations. Blood. 2013; 121 (23) 4749–4752. [PubMed: 23603912]
53. Zhang J, Ding L, Holmfeldt L, et al. The genetic basis of early T-cell precursor acute lymphoblastic leukaemia. Nature. 2012; 481 (7380) 157–163. [PubMed: 22237106]
54. Stock W, La M, Sanford B, et al. What determines the outcomes for adolescents and young adults with acute lymphoblastic leukemia treated on cooperative group protocols? A comparison of Children's Cancer Group and Cancer and Leukemia Group B studies. Blood. 2008; 112: 1646–1654. [PubMed: 18502832]
55. Stock W, Luger SM, Advani AS, et al. Favorable outcomes for older adolescents and young adults (AYA) with acute lymphoblastic leukemia (ALL): early results of U.S. intergroup trial C10403. Blood. 124 (21) 2014;
56. Huguet F, Leguay T, Raffoux E, et al. Pediatric-inspired therapy in adults with Philadelphia chromosome-negative acute lymphoblastic leukemia: the GRAALL-2003 study. J Clin Oncol. 2009; 27: 911–918. [PubMed: 19124805]
57. Patel B, Fielding AG, et al. Peg-Asparaginase During Induction in Adult ALL (UKALL14). Blood. 122 2013;
58. Rytting ME, Thomas DA, O'Brien SM, et al. Augmented Berlin-Frankfurt-Munster therapy in adolescents and young adults (AYAs) with acute lymphoblastic leukemia. Cancer. 2014; 120 (23) 3660–3668. [PubMed: 25042398]

59. O'Brien S, Thomas D, Ravandi F, et al. Results of the hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone regimen in elderly patients with acute lymphocytic leukemia. Cancer. 2008; 113 (8) 2097–101. [PubMed: 18720356]
60. Gökbuget N, Beck J, Brüggemann M, et al. Moderate intensive chemotherapy including CNS-prophylaxis with liposomal cytarabine is feasible and effective in older patients with Ph-negative acute lymphoblastic leukemia (ALL): results of a prospective trial from the German Multicenter Study Group for Adult ALL (GMALL) [abstract]. Blood. 2012. 120.
61. Jabbour E, O'Brien S, Thomas D, et al. Inotuzumab ozogamicin (IO) in combination with low-intensity chemotherapy as front-line therapy for elderly patients with acute lymphoblastic leukemia. Blood. 2014; 124
62. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia (ALL) the greatest benefit is achieved from a matched sibling allogeneic transplant in first complete remission (CR) and an autologous transplant is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the international ALL trial (MRC UKALL XII/ECOG 2993). Blood. 2008; 111: 1827–1833. [PubMed: 18048644]
63. Campana D. Minimal residual disease in acute lymphoblastic leukemia. Hematology Am Soc Hematol Educ Program. 2010. 7–12. [PubMed: 21239764]
64. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). Blood. 2009; 113 (18) 4153–1162. [PubMed: 19141862]
65. Brüggemann M, Raff T, Flohr T, et al. Clinical significance of minimal residual disease quantification in adult patients with standard-risk acute lymphoblastic leukemia. Blood. 2006; 107 (3) 1116–1123. [PubMed: 16195338]
66. Raff T, Gokbuget N, Luschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. Blood. 2007; 109 (3) 910–915. [PubMed: 17023577]
67. Borowitz MJ, Devidas M, Hunger SP, et al. Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study. Blood. 2008; 111 (12) 5477–5485. [PubMed: 18388178]
68. Van der Velden VH, Corral L, Valsecchi MG, et al. Prognostic significance of minimal residual disease in infants with acute lymphoblastic leukemia treated within the Interfant-99 protocol. Leukemia. 2009; 23 (6) 1073–1079. [PubMed: 19212338]
69. Conter V, Bartram CR, Valsecchi MG, et al. Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia: results in 3184 patients of the AIEOP-BFM ALL 2000 study. Blood. 2010; 115 (16) 3206–3214. [PubMed: 20154213]
70. Gökbuget N, Kneba M, Raff T, et al. Adults with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. Blood. 2012; 120 (9) 1868–1876. [PubMed: 22442346]
71. Ribera JM, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. J Clin Oncol. 2014; 32 (15) 1595–1604. [PubMed: 24752047]
72. Nagorsen D, Kufer P, Baeuerle PA, Bargou R. Blinatumomab: a historical perspective. Pharmacol Ther. 2012; 136 (3) 334–342. [PubMed: 22940266]
73. Topp MS, Kufer P, Gokbuget N, et al. Targeted therapy with the T-cell-engaging antibody blinatumomab of chemotherapy-refractory minimal residual disease in B-lineage acute lymphoblastic leukemia patients results in high response rate and prolonged leukemia-free survival. J Clin Oncol. 2011; 29 (18) 2493–2498. [PubMed: 21576633]
74. Topp MS, Gokbuget N, Zugmaier G, et al. Long-term follow-up of hematologic relapse-free survival in a phase 2 study of blinatumomab in patients with MRD in B-lineage ALL. Blood. 2012; 120 (26) 5185–5187. [PubMed: 23024237]

75. Goekbuget N, Dombret H, Bonifacio M, et al. BLAST: a confirmatory, single-arm, phase 2 study of blinatumomab, a bispecific T-cell engager (BiTE) antibody construct, in patients with minimal residual disease B-precursor acute lymphoblastic leukemia (ALL). Blood. 2014; 124
76. Thomas DA, Kantarjian H, Smith TL, et al. Primary refractory and relapsed adult acute lymphoblastic leukemia: characteristics, treatment results, and prognosis with salvage therapy. Cancer. 1999; 86 (7) 1216–1230. [PubMed: 10506707]
77. Tavernier E, Boiron JM, Huguet F, et al. Outcome of treatment after first relapse in adults with acute lymphoblastic leukemia initially treated by the LALA-94 trial. Leukemia. 2007; 21 (9) 1907–1914. [PubMed: 17611565]
78. Gökbuget N, Stanze D, Beck J, et al. Outcome of relapsed adult lymphoblastic leukemia depends on response to salvage chemotherapy, prognostic factors, and performance of stem cell transplantation. Blood. 2012; 120 (10) 2032–2041. [PubMed: 22493293]
79. Topp M, Gokbuget N, Zugmaier G, et al. Phase II Trial of the Anti-CD19 Bispecific T Cell-Engager Blinatumomab Shows Hematologic and Molecular Remissions in Patients With Relapsed or Refractory B-Precursor Acute Lymphoblastic Leukemia. J Clin Oncol. 2014; Dec 20; 32 (36) 4134–4140. [PubMed: 25385737]
80. Topp MS, Goekbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. Lancet Oncol. 2015; 16 (1) 57–66. [PubMed: 25524800]
81. Thomas X. Inotuzumab ozogamicin in the treatment of B-cell acute lymphoblastic leukemia. Expert Opin Investig Drugs. 2012; 21 (6) 871–878.
82. Advani A, Coiffier B, Czuczman MS, et al. Safety, pharmacokinetics, and preliminary clinical activity of inotuzumab ozogamicin, a novel immunoconjugate for the treatment of B-cell non-Hodgkin's lymphoma: results of a phase I study. J Clin Oncol. 2010; 28 (12) 2085–2093. [PubMed: 20308665]
83. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calicheamicin conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. Lancet Oncol. 2012; 13 (4) 403–411. [PubMed: 22357140]
84. Kebriaei P, Wilhelm K, Ravandi F, et al. Feasibility of allografting in patients with advanced acute lymphoblastic leukemia after salvage therapy with inotuzumab ozogamicin. Clin Lymphoma Myeloma Leuk. 2013; 13 (3) 296–301. [PubMed: 23313065]
85. Kantarjian H, Thomas D, Jorgensen J, et al. Results of inotuzumab ozogamicin, a CD22 monoclonal antibody, in refractory and relapsed acute lymphocytic leukemia. Cancer. 2013; 119 (15) 2728–2736. [PubMed: 23633004]
86. Jabbour E, O'Brien S, Huang X, et al. Prognostic factors for outcome in patients with refractory and relapsed acute lymphocytic leukemia treated with inotuzumab ozogamicin, a cd22 monoclonal antibody. Am J Hematol. 2014. Nov 18.
87. Advani AS, Stein AS, Kantarjian HM, et al. A phase II study of weekly inotuzumab ozogamicin in adult patients with Cd22-positive acute lymphoblastic leukemia in second or later salvage. Blood. 2014; 124
88. Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011; 365 (8) 725–733. [PubMed: 21830940]
89. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. N Engl J Med. 2013; 368 (16) 1509–1518. [PubMed: 23527958]
90. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. N Engl J Med. 2014; 371 (16) 1507–1517. [PubMed: 25317870]
91. Lee DW, Shah NN, Stetler-Stevenson M, et al. T cells expressing CD19 chimeric antigen receptors for acute lymphoblastic leukaemia in children and young adults: a phase 1 dose-escalation trial. Lancet. 2014; S0140–6736 (14) 61403–3.
92. Davila M, Riviere I, Wang X, et al. Efficacy and toxicity management of 19–28z CAR T cell therapy in B cell acute lymphoblastic leukemia. Sci Transl Med. 2014; 6 (224)
93. Turtle CJ, Sommermeyer D, Berger C, et al. Therapy of B cell malignancies with CD19-specific chimeric antigen receptor-modified T cells of defined subset composition. Blood. 2014; 124

Table 1

Cytogenetic and molecular abnormalities in ALL

Category	Cytogenetics	Involved Genes	Adults Frequency (%)	Children Frequency (%)
Hyperdiploid			2–15	10–26
Hypodiploid			5–10	5–10
Pseudodiploid	t(9;22)(q34;q11)	*BCR-ABL1*	15–25	2–6
	del(9)(q21–22)	*p15, p16*	6–30	20
	t(4;11);t(9;11); t(11;19); t(3;11)	*MLL*	5–10	<5
	del(11)(q22–23)	*ATM*	25–30 *	15 *
	t(12;21)(p12;q22)	*TEL-AML1*	<1 †	20–25 †
	t(1;19)	*E2A–PBX1*	<5	<5
	t(17;19)	*E2A–HLF*	<5	<5
	t(1;14)(p32;q11)	*TAL1*	10–15	5–10
	t(7;9)(q34;q32)	*TAL2*	<1	<1
	t(10;14)(q24;q11)	*HOX11*	5–10	<5
	t(5;14)(q35;q32)	*HOX11L2*	1	2–3
	t(1;14)(p32;q11)	*TCR*	20–25 ‡	20–25 ‡
	del(13)(q14)	*miR15/ miR16*	<5	<5
	t(8;14); t(8;22); t(2;8)	*C-MYC*	5	2–5
	+8	*?*	10–12	2
	del(7p)	*?*	5–10	<5
	del(5q)	*?*	<2	<2
	del(6q); t(6;12)	*?*	5	<5

* As determined by LOH (loss of heterozygosity).

† As determined by PCR (polymerase chain reaction).

‡ In T-cell ALL, overall incidence <10%.

Table 2

Recent genetic determinants in ALL by lineage

ALL lineage	Cytogenetic aberration	Involved genes	Protein	comments
B-Cell	BCR/ABL+ (Ph+)	IKZF1	Ikaros	Poor outcome. 80% of Ph+ cases
		CRLF2 + the Ig heavy chain locus; or an interstitial PAR1 deletion	CRLF2	5–10% of cases with no molecular rearrangement. Poor outcome. 50% of children with Down syndrome
	"*BCR/ABL -like*"	IKZF1 deletions, rearrangements/mutations in CRLF2, IGH-CRLF2, NUP214-ABL1, in-frame fusions of EBF1-PDGFRB, BCR-JAK2 or STRN3-JAK2, cryptic IGH-EPOR rearrangements		15% of cases. Potential use of TKIs and/or mTOR and JAK2 inhibitors
	Near-hypodiploid	NRAS, KRAS, FLT3 and NF1		70% of cases
	Low-hypodiploid	IKZF2, and by TP53 disruptions, CDKN2A/B locus deletion		91% of cases
	Hyperdiploid	CREBBP		
		NT5C2 mutations	NT5C2	
		TP53 mutations		6% of cases
T-Cell		PICALM-MLLT10, NUP214-ABL1 fusion, EML-ABL1, SET-NUP214 fusion, MLL, NOTCH1, FBW7, BCL11B, JAK1, PTPN2, IL7R, PHF6, RAS/PTEN,		NOTCH1 (>60%) and/or FBW7 (~20%) mutations associated with a favorable outcome. RAS/PTEN and JAK1 usually poor outcome.

Table 3

Monoclonal antibodies in relapsed/refractory ALL

	N (%)			
	Blinatumomab		Inotuzumab	
Parameter	**Pivotal Study, n=36**	**Confirmatory Study, n=189**	**Single dose n=49**	**Weekly n=40**
Overall Response	25 (69)	81 (43)	28 (57)	24 (60)
Salvage Status				
Salvage 1	11 (31)	38 (20)	13 (27)	16 (40)
Salvage 2+	10 (28)	151 (80)	36 (73)	24 (60)
Median survival (months)	9.8	6.1	5.0	9.5

Table 4

Chimeric Antigen Receptor (CAR)-T cells in ALL

Parameter	U-Penn	MSKCC	NIH
Number treated	30	24	21
Median age (years, range)	10 (5–22)	56 (23–74)	13 (1–30)
% CR	90	91	67
% 12-months survival	72	9 months *	50
% severe CRS	27	39	33

* median survival

U-Penn=University of Pennsylvania; MSKCC=Memorial Sloan Kettering Cancer Center; NIH=National Institute of Health; CR=complete response; CRS=cytokine released syndrome