REVIEW

Therapeutic developments in acute lymphoblastic leukemia

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Abstract: The standard treatment of adult-onset acute lymphoblastic leukemia (ALL) is based on trials conducted 20–25 years ago and has remained largely unchanged since that time. Treatments are lengthy and have been extrapolated from successful pediatric regimens. However, adult disease is cytogenetically different from pediatric disease. Adults often have comorbidities that make completing treatment challenging, and outcomes subsequently suffer. Advances in the understanding of cytogenetics and molecular biology have led to the identification of prognostic factors, as well as offering fertile ground for the development of new therapeutics. The current research in ALL focuses on the development of monoclonal antibodies and small molecule inhibitors, as well as increasing sensitivity in monitoring minimal residual disease, improving upon current chemotherapy, and improving stem cell transplantation. This monograph reviews the current standard of care for adult ALL and the innovations in clinical investigation that aim to improve the future for adults who suffer from this disease. The adult population is in great need of similar advances and stands to benefit tremendously from the research discussed in this review. The challenges of sustainable remission and reduced morbidity and mortality in treatment remain to be surmounted. The aggressive efforts of current clinical trials that are investigating novel therapies both alone and with standard treatment offer hope for adults that is slowly beginning to be realized.

Keywords: adult acute lymphoblastic leukemia, Philadelphia chromosome, monoclonal antibodies, molecular pathways

Introduction

Acute lymphoblastic leukemia (ALL) encompasses a heterogeneous group of B- and T-cell neoplasms. While the prognosis in pediatric cases is quite good, with an overall survival (OS) greater than 80%,[4–7] adults do not fare nearly as well, with only about a 35%–40% 5-year event-free survival (EFS).[5,7] This disparity highlights the need for more effective treatment in adults. Traditional cytotoxic chemotherapy plays a significant role in the treatment of ALL and will likely continue to do so for some time. However, it is woefully inadequate in achieving a durable response and long-term survival. More successful treatments are needed to either supplement or perhaps replace traditional chemotherapy. Innovations in the areas of cytogenetics and molecular diagnostics are leading to the development of novel targets and their corresponding therapeutic agents. This review will discuss the epidemiology, etiology, and current management of ALL, as well as new molecular targets and therapeutics in development that have the potential to significantly alter the clinical course of ALL.

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145

Epidemiology and etiology

In 2011, 5730 cases of ALL were diagnosed and 1420 deaths occurred in the North American population. The average lifetime risk of being diagnosed with ALL is approximately 1/1000, with peaks in childhood (age 2–4 years) and over 50 years of age. Men and Caucasians have a slightly higher risk than women and African Americans.[8]

Risk factors for ALL may include exposure to radiation, benzene and other chemicals, and certain viruses. Certain inherited syndromes seem to carry an increased risk of developing ALL including Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, ataxia telangiectasia, and neurofibromatosis.[8,9] Leukemia-specific fusion genes and gene rearrangements have been identified in the neonatal period in patients who subsequently developed ALL. The clinical application of this determination is not yet clear.[10]

Classification and diagnosis

ALL can be classified according to many schemas, but is preferably classified by biologic characteristics instead of morphology. The currently favored classification schema is the World Health Organization criteria, revised in 2008. This system is useful in predicting prognosis and response to treatment. The current subsets of precursor lymphoid neoplasms in the revised World Health Organization criteria are shown in Table 1.

Immunophenotyping of lymphoblasts by flow cytometry and genetic analysis is an essential adjunct to morphologic diagnosis made by bone marrow aspirate and biopsy. Flow cytometric studies reveal lineage-specific markers on leukemic blasts that allow for appropriate diagnosis. Many of these markers are being targeted for therapeutic antibodies and will be addressed in upcoming sections in this review.

Cytogenetics

The role for cytogenetics in adult ALL is not as clear as in childhood ALL. Also, the cytogenetic makeup of childhood ALL is notably different from the adult disease. The Philadelphia chromosome, t(9;22), present in 2%–5% of childhood cases, is far more prevalent in adults; in fact, it is the most common cytogenetic abnormality in this population, at around 25%–30% prevalence.[11,12] Translocation (12;21), hyperdiploidy, and t(4;11) are all more common in children and are seen infrequently in adults. Analysis of cytogenetics allows for the development of stratification paradigms as well as potential targets for novel agents.

Table I Current World Health Organization (WHO) designations of B- and T-cell acute lymphoblastic leukemia (ALL) subtypes with corresponding molecular abnormalities

B- and T-cell ALL subtypes	Molecular marker (frequency in adults)
B lymphoblastic leukemia/lymphoma	NS
B lymphoblastic leukemia/lymphoma, NOS	NS
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities	NS
B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2)	BCR-ABL1 (25%–30%)
B lymphoblastic leukemia/lymphoma with t(v;11q23)	MLL rearranged (10%–13%)
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22)	TEL-AML1 [ETV6-RUNX1] (1%–2%)
B lymphoblastic leukemia/lymphoma with hyperdiploidy	(7%–9%)
B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid ALL)	(2%)
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)	IL3-IGH
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3)	E2A-PBX1 [TCF3-PBX1] (3%–4%)
T lymphoblastic leukemia/lymphoma	NOTCH1 (50%)
Karyotypes not associated with WHO designation	
del(11)(q22)	ATM
t(q4q11–q13)	TCRα and TCRδ
del(9)(p21–22)	CDKN2A and CDKN2B
t(1;14)(p32;q11)	TAL-1 (12%)
t(10;14)(q24;q11)	HOX11 (8%)
t(8;14), t(8;22), t(2;8)	c-MYC (4%)
t(14q32)	IGH, BCL11B
Extra chromosome 9q	NUP214/ABL
del(13)(q14)	miR15/miR16
t(1;19), t(17;19)	TCF3-PBX1, E2A-HLF
del(5)(q35)	HOX11L2 (1%)
t(5;14)(q35;q32)	HOX11L2 (1%)
del(9)(q32)	TAL-2
del(12p) or t(12p) (more common in pediatrics)	ETV6-RUNX1

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Abbreviation: NOS, not otherwise specified; NS, not significant.

NOTCH1 (Notch homologue 1, translocation-associated)[6] is detected in the majority of human T-cell ALLs.[4,13] This gene regulates transcription of genes involved in T-cell development, including the *MYC* oncogene.[14] T-cell ALL has been induced in animal models with constitutive *NOTCH1* expression and is mediated through gamma secretase, a membrane-associated enzyme.[15] This provides the opportunity for a therapeutic target through inhibition,[15] which will be discussed later in this review.

Deletion of *IKZF1*, the gene encoding the Ikaros transcription factor, has been found to be associated with the

development of Philadelphia chromosome–positive (Ph+) ALL. Ikaros is a zinc-finger nuclear protein required for lymphoid development. Genome analysis of ALL patients revealed an *IKZF1* deletion rate of 83.7% in *BCR-ABL1* ALL.[16]

Prognostic factors

Prognostic factors have evolved with the changes in molecular diagnostics and cytogenetics that continually shape the way ALL is viewed. As treatments develop that target specific subtypes of ALL, prognosis is often affected. For example, the presence of the Philadelphia chromosome, t(9;22) associated with the *BCR-ABL* rearrangement, is the most common cytogenetic abnormality in adults and has traditionally been a poor prognostic factor. However, treatment with tyrosine kinase inhibitors (TKIs) such as imatinib and dasatinib have improved remission rates in young patients to >90%.[17]

Unfavorable prognostic features include (1) age, with adults over 50 years of age and infants under the age of 1 having a less favorable outcome,[9,18–22] (2) higher degree of leukocytosis (>30,000 cells/mm³),[18–22] (3) higher lactate dehydrogenase (LDH) levels,[22] (4) more than one course[18] or more than 4 weeks[9,19] to first complete response (CR), (5) central nervous system (CNS) involvement,[18,20,21] (6) persistent minimum residual disease (MRD),[19,23] and (7) cytogenetic abnormalities including *BCR-ABL*.[22,24]

Management issues

The management of ALL prior to or during treatment involves a number of issues that can be serious and even life threatening. These complications fall into four broad categories: (1) metabolic, (2) hematologic, (3) infectious, and (4) treatment related.

The most common and potentially most serious metabolic complication is tumor lysis syndrome (TLS). Patients are at risk for developing TLS spontaneously if disease burden is high and most certainly upon institution of treatment. Caused by products of cell lysis, TLS is characterized by the derangements that follow: increased phosphate and potassium from intracellular contents and decreased calcium from aggregation with phosphate. Urate levels become very high secondary to purine catabolism and can lead to urate nephropathy with kidney failure.[25] Risk factors for TLS include elevated LDH levels, elevated white blood cell (WBC) count, preexisting renal failure, oliguria, elevated baseline uric acid levels, and the use of cytoreductive therapy.[25] A predictive model developed for TLS in acute myeloid leukemia (AML) in a single-center, retrospective cohort study found these risk

factors, as well as gender and a history of chronic myelomonocytic leukemia, to be significant predictors.[26] Prevention of TLS is the ideal clinical scenario, and should include the following measures: adequate hydration, avoidance of nephrotoxic drugs, and the use of either a xanthine oxidase inhibitor or recombinant urate oxidase.[25,27] Laboratory studies including serum creatinine, potassium, phosphate, calcium, LDH, and uric acid levels should be followed two to three times per day to detect the development of TLS as quickly as possible. Treatment may involve hemodialysis, transfer to the intensive care unit, and involvement of other subspecialists such as cardiology for arrhythmia management.

Hematologic complications include disseminated intravascular coagulation (DIC), hyperleukocytosis, and cytopenias. DIC, characterized by systemic activation of coagulation, massive consumption of coagulation factors, and deposition of fibrin in the bloodstream, can result in both major bleeding complications and thrombotic or embolic complications. It is associated with the expression of procoagulant, fibrinolytic and proteolytic properties of leukemic cells as well as cytotoxic therapy, particularly L-asparaginase.[28,29] Between 25% and 65% of patients may develop DIC during induction chemotherapy,[30–32] with 10%–20% presenting with DIC.[31,33] Patients present with hypofibrinogenemia (<100 mg/dL), prolongation of clotting times, and elevated D-dimer value. Patients may also have concomitant thrombocytopenia, but this is just as likely to be due to marrow infiltration or platelet consumption.[28] Treatment of DIC rests upon the treatment of the underlying malignancy but it is managed with supportive care in the interim.

Hyperleukocytosis has been associated with hemorrhage, DIC, TLS, pulmonary leukocytosis, and neurologic complications and mortality rates as high as 40%.[34] Pulmonary symptoms are common and can lead to severe hypoxemia. Patients should be on continuous pulse oximetry monitoring if there are any concerns for pulmonary leukostasis. Neurologic symptoms can include headache, blurred vision, or gait abnormalities and patients exhibiting these symptoms should undergo leukoreduction. If the patient's WBC count is <400,000, chemical reduction with hydroxyurea is acceptable and will reduce the blast burden quite quickly. In patients with more severe hyperleukocytosis, leukapheresis may be necessary. As with all critically ill patients, the risk-benefit ratio must be evaluated before beginning any invasive procedure.

Cytopenias are a common complication of both the disease and the treatment. Patients are most likely to have spontaneous bleeding at a platelet count below 5000–10,000/mm³

and a transfusion threshold of 10,000 platelets/μL for stable patients is reasonable.[35] A threshold of 20,000/mm³ is appropriate for febrile patients, those with active infection, coagulopathy, and hyperleukocytosis. DIC or active bleeding warrants a platelet count of 50,000/mm³, if possible. Packed red blood cell transfusion triggers vary based on patient scenario (ie, symptomatic anemia). Most patients can tolerate a threshold between 7 and 9 g/dL and the decision to transfuse is generally made based on the patient's overall clinical situation. However, when a patient first presents, anemia should not be corrected with packed red blood cell transfusion before hyperleukocytosis, as this can lead to increased viscosity and worsening of the sequelae of the elevated WBC count. It should be noted that while transfusions are essential for the treatment of leukemic patients, transfusions do carry risk, including transfusion reaction (both acute and delayed) and development of antibodies that can limit the ability to transfuse the patient in the future.

In the acute leukemia population, patients are at high risk of infection due to defects in the immune system; this, combined with cytotoxic treatment, makes infections the leading cause of death in ALL. Neutropenic fever is a common occurrence in the leukemia population and is almost always managed with inpatient admission and intravenous antibiotics directed initially against gram-negative organisms. Additional antibiotics can be added at the time of admission for special circumstances such as a previous history of infection or colonization with a non-gram-negative organism. Antibiotic coverage should be expanded to cover gram-positive organisms if a patient becomes hemodynamically unstable, develops a radiographically evident pneumonia, or develops a skin or soft-tissue infection and in cases of severe mucositis. Patients who remain febrile for 4–7 days while on appropriate gram-positive and gram-negative coverage should receive antifungal coverage targeted at mold and a thorough investigation with computed tomography scanning to determine the etiology. Fungal infections can be aggressive and are a source of morbidity and mortality in this population.

Treatment

Initial treatment for ALL traditionally consists of induction phase chemotherapy, the goal of which is to reduce the burden of disease as quickly as possible and to allow for restoration of normal or at least adequate bone marrow function. At the completion of induction, one hopes for a reduction in measurable disease to levels undetectable by microscopic evaluation (ie, 10⁹ cells). Induction chemotherapy is then followed by a consolidation and/or maintenance phase, possibly including hematopoietic stem cell transplantation (HSCT); this phase of treatment is increasingly becoming tailored to molecular markers and prognostic factors.

Cytotoxic chemotherapy regimens are currently the standard of care in the induction phase of treatment for adult ALL. Several regimens are in use but none has been proven more efficacious than the others in clinical trials.[6] Because of the large number and permutations of specific drugs that have been evaluated in trials, critical analysis of combinations is challenging. The most common drug regimens used include vincristine, an anthracycline, and a steroid (usually dexamethasone). Additional drugs added include asparaginase, high-dose methotrexate, cytarabine, mitoxantrone, and cyclophosphamide, although this list is not exhaustive.[36]

Cancer and Leukemia Group B (CALGB) study 7612 compared vincristine, prednisone, and L-asparaginase with or without daunorubicin. Although it was a relatively small study, patients receiving daunorubicin exhibited a CR rate of 83% (38/46 patients), compared with 47% (25/53 patients) in the non-anthracycline arm ($P = 0.003$).[37] This was a landmark study in leading to the addition of anthracyclines to standard induction chemotherapy in ALL.

CALGB study 8811[38] was a phase II trial that evaluated both a five-drug intensive regimen and the impact of several biological and clinical features on the course of the disease. In all, 197 patients were treated with cyclophosphamide, daunorubicin, vincristine, prednisone, and L-asparaginase. A CR was achieved in 85% of all patients and in 94% of patients younger than 30 years of age. After median follow-up of 43 months, median survival was 36 months, with a median remission duration of 29 months.

Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) is a regimen used by Kantarjian et al[18] that includes the traditional vincristine, doxorubicin, and dexamethasone with the addition of hyperfractionated cyclophosphamide, as opposed to bolus dosing. The total regimen consists of eight cycles: hyper-CVAD alternating with high-dose methotrexate and cytarabine. Patients in the aforementioned Kantarjian study at risk for CNS disease received CNS prophylaxis with 16 intrathecal treatments. Patients were compared with historical controls who had been treated with vincristine, doxorubicin, and dexamethasone alone.[39] Ninety-two percent of the intrathecal-treated patients achieved a complete remission; in comparison, the patients treated with vincristine, doxorubicin, and dexamethasone alone achieved a CR of 75% ($P < 0.001$). Median survival was 35 months, with a 5-year survival rate of 39%.[39]

A study by Weiss et al[40] examined the effect of cytarabine with high-dose mitoxantrone, as it was believed by the authors that additional variation on the currently used drug regimens was unlikely to produce a significantly different outcome from previous trials. It was also hypothesized that this combination may lead to an earlier CR, thus predicting a more favorable outcome. Time to CR was indeed more rapid with this regimen when compared with historical controls; however, the percentage of subjects achieving CR and median survival was not significantly different between the two groups.

Regardless of the induction regimen employed, achieving CR prior to postremission maintenance therapy is highly predictive of OS. An international ALL trial (Eastern Cooperative Oncology Group [ECOG] study 2993) demonstrated that patients who did not achieve CR at the end of induction had an OS rate of only 5% compared with 45% at 5 years in those who went into complete remission.[20] This trial, as did many others, validated the significance of several prognostic factors in predicting clinical outcomes in ALL.

Post-induction therapy

Upon completion of intensive induction therapy and restoration of the normal marrow, patients must undergo some form of consolidation therapy to treat the residual leukemia. In some regimens patients will undergo extended intensification or re-induction prior to moving to consolidation therapy.[41] Delayed intensification has been shown to improve outcome in patients with intermediate-risk ALL.[42] As is the case with induction therapy, there is no consensus on the optimal consolidation regimen. Most consolidation regimens contain a continuation of some chemotherapeutic drugs used in induction as well as antimetabolites such as high-dose cytarabine and high-dose methotrexate with or without mercaptopurine. The concept of "re-induction" or delayed intensification with a recapitulation of the initial induction treatment has been used in the Berlin-Frankfurt-Munster trials.[44] This has been largely evaluated in children and adolescents.

Several large leukemia consortia have developed trials to evaluate various combinations of drugs, although there has not been a direct comparison among the regimens. The CALGB published results of a phase II multicenter trial that treated adults with an intensified pediatric regimen.[38] Patients had improved CR rates (94%) and improved survival (median survival, 36 months) when compared with other large, multicenter trials. The Gruppo Italiano Malattie Ematologiche dell'Adulto randomized almost 400 patients to

receive intensification plus maintenance versus maintenance alone. There was no difference at 8 years, with a 36% disease-free survival (DFS) in the intensification arm versus a 37% DFS in the maintenance-only arm. However, only 35% of patients in the maintenance-only arm completed treatment secondary to toxicity issues.[46]

The Dutch-Belgian HOVON Cooperative Group recently published results of a phase II trial that evaluated a pediatric ALL regimen in adults under the age of 40. Fifty-four patients with a median age of 26 were treated with asparaginase, steroids, methotrexate, and vincristine. CR was achieved in 49 patients, with estimated 2-year EFS and OS of 66% and 72%, respectively, for all patients. Rates were higher for standard-risk patients (EFS and OS of 87%) and lower for high-risk patients (2-year EFS and OS of 43% and 57%, respectively), as would be expected. It was thought that major toxicity was related to infections and not the drugs per se.[44] The CALGB has an ongoing trial (10403) that also hopes to show increased efficacy with tolerable toxicity in young adults receiving intensive pediatric regimens.

Ph+ disease

Ph+ ALL is designated by the BCR-ABL fusion gene, a result of the translocation between the BCR gene on chromosome 22 with the ABL1 (Abelson murine leukemia viral onco-gene homolog 1) gene on chromosome 9 [t(9;22)(q34;q11)]. BCR-ABL fusion gene is the most common cytogenetic abnormality in ALL and can be detected in 20%–30% of adult ALL patients.[46–49] Until recently, Ph+ ALL was associated with a poor prognosis (5-year OS, 10%–20%),[50] with the greatest hope for success via allogeneic HSCT. As compared with non Ph+ ALL, CR rates in Ph+ ALL with traditional chemotherapy range from 50% to 90%.[49] Prolonged CR has been found to be far worse in patients with Ph positivity (11% at 3 years versus 50%–70%, depending on genetic results);[38] 13% chance of disease free survival versus 47% in Ph negative disease.[48] In the international ALL study ECOG 2993, outcomes for Ph+ patients undergoing stem cell transplantation (SCT) were superior to those receiving chemotherapy alone. Five-year survival was 44% with a sibling donor, 36% with an unrelated donor, and 19% if given chemotherapy alone. The difference between the sibling donor and the matched unrelated donor transplantation was not statistically significant, but the outcome after any allogeneic transplantation versus chemotherapy alone significantly favored transplantation (OS, $P = 0.001$; EFS, $P < 0.001$; relapse-free survival, $P < 0.001$).[51] Patients who were not considered good candidates (eg, lack of donor availability or poor performance status) for transplantation

had little hope. However, the development of the TKI imatinib changed the landscape of Ph+ disease radically. Now that the achievement of a CR in this disease is approximately 95%,[46] the questions are focused on which TKI to choose and when and how to maintain a durable remission.

Numerous trials have been undertaken to evaluate the use of TKIs in the relapsed or primary refractory setting (see Table 2). These studies have demonstrated the possibility for both hematologic and cytogenetic response with the use of TKIs. Subsequently, several trials combined chemotherapy with TKIs as frontline therapy, but with the use of historical controls for the chemotherapy-alone arm. Thomas et al compared imatinib plus hyper-CVAD with historical controls and found 93% of patients on combined therapy achieved a complete hematologic response (CHR) after a median of 21 days. Three-year survival rates were significantly higher in the imatinib group, with DFS of 62% versus 14% for controls and OS of 55% versus 15% for controls ($P < 0.001$ in both cases). The question of how to administer imatinib (either concomitantly with chemotherapy or in alternation) has been addressed by two studies.[52,53] Both found a statistical advantage to the concurrent administration of imatinib during induction and consolidation. A subset (267 Ph positive patients) of the ECOG 2993 study demonstrated similar findings, with a higher CHR in patients who started

imatinib during induction instead of delaying to consolidation (91% versus 81%, respectively) but rates of transplantation and 3-year survival were similar with or without the addition of imatinib.

One of the first trials to compare single-agent imatinib with traditional chemotherapy in the first-line setting was undertaken by the German Multicenter Study Group for Adult ALL (GMALL).[54] In this study, 55 elderly patients with Ph+ ALL from 32 centers were randomized (after having received a pre-phase chemotherapy with dexamethasone, cyclophosphamide, and methotrexate) to receive induction therapy with either imatinib or age-adapted chemotherapy with a multidrug regimen administered during the induction phase. All patients who completed remission induction therapy received imatinib in combination with all successive treatments (consolidation, re-induction, and further consolidation). Response to induction was superior in the imatinib arm, with an overall CR of 96.3% versus 50% in the chemotherapy-alone arm ($P = 0.0001$). Patients who were refractory to chemotherapy or who had achieved only a partial response (n = 11) were crossed over to imatinib. Nine of these eleven patients achieved a CR with imatinib. There were no deaths in the imatinib arm, compared with two deaths during induction with chemotherapy. Remission duration was longer in patients who achieved an undetectable BCR-ABL

Table 2 Early trials evaluating the efficacy of the tyrosine kinase inhibitors

Protocol	Disease	Response rate	Subjects (N)	Other outcomes	References
Imatinib 300–1000 mg daily (dose-finding study)	Ph+ ALL or CML in blast crisis; relapsed or primary refractory	CHR: 20%	20	Median time to relapse: 58 days	Druker et al[102]
Imatinib 400 or 600 mg daily	Ph+ ALL primary refractory or relapsed after chemotherapy or SCT	CHR: 6% CCyR: 17%	48	Median PFS: 2.2 months Median OS: 4–9 months 6-month OS: 40%	Ottmann et al[104]
Dasatinib 35–120 mg BID (dose-finding study)	Ph+ ALL with resistance or intolerance to imatinib	CHR: 70% MCyR: 80% CCyR: 30%	10	90% relapsed in median of 4 months	Talpaz et al[104]
Dasatinib 70 mg BID	Ph+ ALL with imatinib resistance or intolerance and refractory or relapsed	CHR: 35% MCyR: 56% CCyR: 54%	46	Median PFS: 3.3 months 24-month OS: 31%	Ottmann et al; Porkka et al[105,106]
Nilotinib 50–1200 mg daily (dose-finding study)	Ph+ ALL with resistance to imatinib	Partial HR: 8% CMR: 8%	13	Not reported	Kantarjian et al[107]
Nilotinib 400 mg BID	Ph+ ALL with imatinib resistance (including MRD) or intolerance and relapsed or refractory	CHR: 24% MCyR: 51% CCyR: 34%	41	Not reported	Ottmann et al[108]
Bosutinib 400–600 mg daily	Ph+ ALL following resistance or intolerance to imatinib and other tyrosine kinase inhibitors	CHR: 15% MCyR: 18%	17	Not reported	Gambacorti-Passerini et al[109]

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Abbreviations: ALL, acute lymphoblastic leukemia; BID, twice a day; CCyR, complete cytogenetic response; CHR, complete hematologic response; CML, chronic myeloid leukemia; CMR, complete marrow response; HR, hematologic remission; MCyR, major cytogenetic response; MRD, minimum residual disease; OS, overall survival; Ph+, Philadelphia chromosome positive; PFS, progression-free survival; SCT, stem cell transplantation.

transcript. A second study in the elderly, by the Gruppo Italiano Malattie Ematologiche dell'Adulto, combined imatinib with prednisone in induction and demonstrated a similarly high CR with good tolerance but patients had a high relapse rate, with median remission duration of only 8 months.[56]

In the post-allogeneic HSCT setting, TKIs have been studied in the setting of molecular MRD, a harbinger of relapsed disease. A prospective, multicenter study showed that in patients with detectable BCR-ABL transcripts following transplant, imatinib was able to put 52% of patients into a complete molecular response within 3 months. Patients who went into a complete cytogenetic response had a 12-month DFS of 91%, compared with 8% in those who had persistent MRD.[57]

Dasatinib and nilotinib have both been evaluated in the setting of Ph+ ALL. Both TKIs are more potent than imatinib (in vitro), but dasatinib is capable of inhibiting both the active and the inactive conformation of the BCR-ABL translocation.[58] Additionally, dasatinib penetrates the CNS, albeit at low levels, but is not a substrate for P-glycoprotein, an efflux pump in the blood – brain barrier – imatinib, on the other hand, is.[59] Dasatinib has been shown to induce a CHR in imatinib-resistant patients (except for those with T315I mutations) in 6 months.[60] In a phase II study of first-line induction treatment with single-agent dasatinib, 100% (n = 53) of adult patients with Ph+ ALL experienced a CHR, with a median time to CHR of 23 days.[61] Median OS was 30.8 months, with 42.9% of patients free of relapse at 20 months. No patients relapsed during induction with dasatinib. This study illustrates the feasibility of using a single-agent TKI in the induction phase in the absence of cytotoxic chemotherapy.

Nilotinib has been evaluated as a single agent (Table 2), and is currently under investigation as an adjunct to chemotherapy in Ph+ ALL.[62] Fifty patients received nilotinib with induction chemotherapy in the form of vincristine, daunorubicin, and prednisolone. Ninety percent of patients achieved a CHR and 54% achieved a molecular response at the time of CHR. Nilotinib was well tolerated, with the most common adverse effect being grade 3 reversible jaundice. At a median follow-up of 17.4 months, relapse-free survival, EFS, and OS were 71.1%, 49.9%, and 66.2%, respectively. For those patients who are resistant to or intolerant of imatinib, nilotinib is a potential option.

Newer TKIs are currently under investigation (Table 3). The PACE (Ponatinib Ph+ ALL and Chronic myeloid leukemia Evaluation) trial is examining ponatinib in patients with chronic myeloid leukemia or Ph+ ALL resistant or intolerant to dasatinib or nilotinib with the T315I mutation.[63] This is an international, open-label, phase II, single-arm

Table 3 New tyrosine kinase inhibitors under investigation for Philadelphia chromosome–positive acute lymphoblastic leukemia

Drug (manufacturer)	Target	Phase
Bosutinib [SKI-606] (Wyeth)	BCR-ABL, SRC	I/II
INNO-406 (Innovive Pharmaceuticals)	BCR-ABL, Lyn kinase	I
MK-0457 (Merck)	BCR-ABL, activity against T315I, aurora kinases, JAK2, FLT3	II
XL228 (Exelixis)	BCR-ABL, activity against T315I, aurora kinases, IGFR1, SRC, FGFR1–3	I (terminated)
KW-2449 (Kyowa Hakko Kirin)	BCR-ABL, activity against T315I, aurora kinases, FLT3	I (terminated)
PHA-739358 (Nerviano Medical Sciences)	Activity against T315I, aurora kinases	I
AS703569 (Merck Serono)	Activity against T315I, aurora kinases	I
ONO12380 (Onconova Therapeutics)	BCR-ABL, SRC, activity against T315I, PDGFR	Preclinical
MLN8237 (Millenium Pharmaceuticals)	Activity against T315I, aurora kinases	Preclinical
AP23464 (Ariad Pharmaceuticals)	BCR-ABL, SRC family kinases	Preclinical

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Abbreviations: FGFR1–3, fibroblast growth factor receptors 1–3; FLT3, FMS-like tyrosine kinase 3; IGFR1, insulin-like growth factor receptor 1; JAK2, Janus kinase 2; PDGFR, platelet-derived growth factor receptor.

study to establish efficacy and safety of this alternative TKI. Thus far, 17% (67) of patients have experienced at least one adverse effect, and 37% of those ALL patients resistant or intolerant to dasatinib or nilotinib had a major hematologic response, with 27% of T315I patients exhibiting a major hematologic response. More data are needed to determine the role of ponatinib in the treatment of Ph+ ALL.

SCT

The most intensive and potentially curative treatment for ALL is allogeneic HSCT. Patients who are considered high risk (older age, Ph+ disease, leukocytosis) have seen benefit from allogeneic transplantation in first remission, despite the expected toxicity frequently associated with this therapy.[24,53,64,65] SCT as a consolidation modality in standard-risk ALL is a controversial subject. The most well-known study to have evaluated both autologous and allogeneic SCT is the international ALL study ECOG 2993, which enrolled 1929 patients aged between 15 and 59 years. Patients underwent induction and then were either assigned to allogeneic transplant, if a matched sibling donor was available,

or randomized to chemotherapy or autologous HSCT. The high-risk criteria for this trial were defined by age >35 years, leukocytosis ($\geq 30 \times 10^9$/L in B-lineage and 100×10^9/L for T-lineage ALL), and Ph positivity. Patients fared well, with an overall CR rate of 90% and 5-year survival of 43%. Ph-negative (Ph–) patients with a matched donor had a 5-year survival of 53%, compared with 45% in those with no matched donor ($P = 0.02$). Similarly, standard-risk patients with a donor had superior survival to those with no donor (62% versus 52%, respectively, at 5 years; $P = 0.02$). However, high-risk patients suffered a degree of transplantation-related toxicity, to the extent that survival rates were not improved significantly with a matched sibling (41% [no matched donor] versus 35% [matched donor]; $P = 0.2$). Autologous transplant was not found to produce superior EFS or OS when compared with postremission chemotherapy ($P = 0.02$ and $P = 0.03$, respectively).[66] Haploidentical transplantation is an area of clinical investigation that may offer another alternative for patients who are without a fully matched donor. The graft versus leukemia effect is slightly more pronounced in a haploidentical transplantation, which may offer both greater duration of remission and better OS. There are no clear indications at this time regarding which patients are ideal for undergoing transplantation; however, all adult ALL patients should be referred to a transplant center for evaluation.

Non-myeloablative SCT is a potential option for patients who are not eligible for standard allogeneic transplant (eg, elderly patients or high-risk patients with significant comorbidities) because of the high risk of morbidity and mortality.[67] Non-myeloablative conditioning was examined in a multicenter analysis of 51 patients who underwent allogeneic SCT with a regimen of fludarabine for 2 days and 2 Gy of total body irradiation for 1 day. All patients were high risk and 45 patients were over 18 years of age; approximately half were Ph+. Forty-three percent of patients had relapsed at a median of 5 months posttransplant, with a median time to death from progression of 4 months. Patients beyond first CR had an increased risk of relapse compared with those in first remission (hazard ratio, 3.9; $P = 0.002$) and an 8% 3-year OS rate. The estimated OS rate among all patients was 34%, similar to that of patients who have undergone standard chemotherapy. Sixteen patients were over 60 years of age – this is a population who would be strongly considered for a reduced-intensity conditioning regime. Four of the 16 patients had disease relapse and six died of non-relapse-related causes. Ph+ patients in this group (n = 7) had an estimated 3-year OS of 57%, highlighting the benefit of TKIs in improving outcomes.[68]

In the Ph+ patient, TKIs should be started with induction and consolidation and then followed by SCT. Because of the success with TKIs, more Ph+ patients are able to undergo transplantation in first remission. Myeloablative transplantation following the combination of induction chemotherapy and TKI has led to 3-year OS rates of 55%–65%, an impressive rate for adults.[69]

Novel therapies

Given the overall results of conventional chemotherapy in adults, it is quite clear that patients are in dire need of more effective therapy. As has been demonstrated, induction regimens can bring most adult patients into a complete remission but adults are at particularly high risk for relapse when compared with the pediatric population. Therefore, therapy that aims to keep the disease at bay once in remission is highly sought after. There are a number of different categories of novel therapies and several of them will be discussed here.

Monoclonal antibodies

Surface antigen expression in ALL blasts is a characteristic that has been used to categorize disease when cells are analyzed by flow cytometry. Since these markers are now easily identified, this fact has been exploited to develop monoclonal antibody therapy. The surface antigens CD19, CD20, CD22, CD33, and CD52 have all been targeted with directed therapy in the form of antibodies.

CD19 is expressed during the early stages of B-cell maturation and development and is therefore found in almost all precursor-B leukemias. Blinatumomab is a bispecific antibody that is targeted to CD19 and CD3. The two binding sites allow for the recruitment of CD3+ cytotoxic T-cells and the destruction of CD19+ tumor cells. Initially studied in refractory non-Hodgkin's lymphoma,[70] it was subsequently evaluated in a small GMALL study of adult patients with B-precursor ALL and detectable MRD. Of 21 patients, an 80% response rate was seen after treatment with blinatumomab.[71]

CD20 is a B-lymphocyte-specific membrane phosphoprotein that is expressed on the surface of mature B-cells and a variable percentage of ALL cells. CD20 has been found to have an unfavorable impact prognostically in a group of 253 adult ALL patients studied at MD Anderson Cancer Center.[72] The monoclonal antibody directed against this antigen, rituximab, has been evaluated in a study of CD20+/Ph– B-precursor ALL patients when added to chemotherapy during induction and consolidation. Of 185 patients,

117 received rituximab and were compared with 70 patients who had previously received identical chemotherapy. In standard-risk patients (133/185), there was no difference between chemotherapy alone and with the addition of rituximab in CR (93% and 94%, respectively), early rates of death (4% and 5%, respectively), or relapse (2% and 1%, respectively). However, decrease in measured MRD was faster in patients who were treated with rituximab, with MRD $< 10^4$ (molecular CR) at day 21 of 60%, compared with 19% for those not treated with rituximab. This persisted at week 16 (89% and 57%, respectively) and the probability of a continued CR at 3 years remained higher in rituximab-treated patients. Of the high-risk patients (52/185) who proceeded to transplantation, OS was improved in the rituximab arm.[73] A second GMALL study in older adults administered rituximab prior to eight cycles of dose-reduced chemotherapy. Twenty-six patients were evaluated and found to have a CR rate of 63%. OS at 1 year was 54%.[74]

MD Anderson Cancer Center has combined rituximab with chemotherapy in both the under 60 and the over 60 year old population. A modified hyper-CVAD regimen with the antibody produced a CR rate of 95% in the younger than 60 group and 88% in the elderly. Three-year CR duration was improved significantly in younger patients but not in older patients. The number of deaths in the older, CD20+ group was higher and related to infections, cardiovascular events, and secondary myelodysplastic syndrome. The morbidity associated with this regimen in this population led the investigators to conclude rituximab was not beneficial.[75]

Ofatumumab, another anti-CD20 antibody, binds with greater avidity than rituximab and at a different site. A phase II trial is being conducted at MD Anderson Cancer Center that combines ofatumumab with hyper-CVAD as frontline therapy in ALL.

CD22 is expressed in the great majority of B-precursor ALL. Epratuzumab, a humanized antibody, modulates B-cell signaling by binding to the extracellular domain of CD22. Although primarily studied in pediatrics, there are currently phase I and II clinical trials underway internationally to establish efficacy of epratuzumab either alone or in combination with chemotherapy. In the United States, the National Cancer Institute and Southwestern Oncology Group are sponsoring a phase II trial that evaluates epratuzumab with clofarabine and cytarabine in relapsed or refractory Ph– ALL.

CD52 is found on both B- and T-lymphocytes and has been a target of treatment in other settings (chronic lymphocytic leukemia, cutaneous T-cell lymphoma, and peripheral T-cell lymphoma) by the antibody alemtuzumab (Campath®).

A number of studies that examine alemtuzumab in the relapsed or refractory setting are either completed or have finished recruiting. In the CALGB 10102 study, interim results of the phase I study demonstrated encouraging improvement in DFS. During this dose-escalation study, patients in remission were given single-agent alemtuzumab three times per week for 4 weeks as the fourth phase in an eight-phase treatment regimen. Although patients had an increase in the incidence of viral infections, addition of the drug was found to be feasible and did provide reduction in MRD. The phase II portion of the study, an efficacy study, is underway.[76]

Gemtuzumab ozogamicin (Mylotarg®) is an antibody targeted against CD33. After an increase in deaths in AML patients receiving gemtuzumab, the drug was withdrawn from the commercial market in 2010. However, it is currently being evaluated in clinical trials at lower doses in the treatment of hematologic malignancies, and may be used therapeutically again in the future.

Molecular pathways

Greater analysis of the molecular basis of leukemia has led the field of novel therapeutics toward the development of more precisely targeted agents in ALL. The ideal treatment in this realm would have fewer side effects than traditional chemotherapy and would have the advantage of targeting the specific molecular abnormality in any given leukemic subtype. These agents target receptors and kinases and have intranuclear activity as well. There are a growing number of clinical trials employing these agents, with much anticipation regarding their performance.

Modifications to gene promoter regions have been found to play an important role in the development of acute leukemia. DNA alterations that affect gene expression can occur without an impact on the nucleotide sequence, a process known as epigenetic modification. These alterations take place via several mechanisms, two of which have been targeted with novel agents. Histone deacetylase (HDAC) inhibitors prevent the removal of acyl groups from histone proteins and disrupt the nucelosome structure.[77] HDAC inhibitors have been found to induce apoptosis in drug-resistant leukemic cells.[78] In Ph+ ALL, HDAC inhibitors also lead to increased expression of several apoptosis-associated proteins.[79] Vorinostat (suberoylanilide hydroxamic acid) currently carries US Food and Drug Administration approval for refractory cutaneous T-cell lymphoma, based on efficacy in phase I/II trials. Tolerability has been demonstrated for several other HDAC inhibitors (see Table 4) and phase II

Table 4 Targeted agents for acute lymphoblastic leukemia currently under investigation

Target	Agent	Clinical trial	Clinical target
HDAC inhibitors	Vorinostat (SAHA)	Yes	ALL
	Depsipeptide/romidepsin (FK228)		
	Panobinostat (LBH589)		
	Valproic acid		
DNA methyltransferase inhibition	Decitabine	Yes (with vorinostat)	ALL relapsed
	Temozolomide	Yes (with veliparib)	Acute leukemia
	Azacytidine	Yes	ALL
mTOR inhibition	Sirolimus	Yes	ALL
	Temsirolimus	Yes	–
	Everolimus	Preclinical	ALL
Gamma secretase inhibition, required for NOTCH1 signaling	RO4929097, BMS906024, PF03084014	Yes	T-cell ALL
HSP70 downregulation, PI3K/AKT inhibition	Reservatrol	Not yet	ALL
FMS-like tyrosine kinase 3 inhibition	Lestaurtinib, midostaurin; tandutinib, sunitinib, IMC-EB10, sorafenib	Yes	*MLL*-rearranged, hyperdiploid
DNA polymerase and ribonucleotide reductase; disrupts mitochondrial membrane	Clofarabine	Approved	ALL, high risk, pediatric
Ribonucleotide reductase, DNA synthesis	Nelarabine	Approved	T-cell ALL
Anti-CD22	Epratuzumab	Yes	CD22 positive
Anti-CD52	Alemtuzumab (Campath®)	Yes	CD52 positive
Anti-CD33	Gemtuzumab ozogamicin	Withdrawn in 2010	–
Aurora kinase	MK-0457/tozasertib	One completed, two terminated	BCR-ABL positive
Farnesyltransferase inhibition	Lonafarnib	Yes	ALL
	Tipifarnib	Yes	ALL
Proteasome inhibition	Bortezomib	Yes	ALL
BCL-2	Oblimersen (Genasense®)	Yes	Acute leukemia
CXCR4	AMD-3100 (Mozobil®)	Yes	ALL

Abbreviations: ALL, acute lymphoblastic leukemia; BCL-2, B-cell lymphoma 2; CXCR4, CXC chemokine receptor type 4; HDAC, histone deacetylase; HSP70, heat shock protein 70; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3 kinase; SAHA, suberoylanilide hydroxamic acid.

trials combining HDAC inhibitors with chemotherapy are underway at several national centers.

The second class of drugs associated with epigenetic modifications is the DNA methylase inhibitors. Hypermethylation of cytosine clusters in the promoter region of tumor suppressor genes leads to gene silencing and tumor proliferation. Some of these regulatory genes have been implicated in a subset of Ph– adult ALL.[80] Decitabine is an inhibitor of methylation that has been tested in phase I clinical trials in the setting of relapsed/refractory ALL and is currently being evaluated in combination with the HDAC inhibitor vorinostat in several ongoing clinical trials.

Kinase inhibitors

Several kinases have shown promise as targets in ALL. Drugs that are being investigated to act on kinases include mammalian target of rapamycin (mTOR) inhibitors, FMS-like tyrosine kinase-3 (FLT3) inhibitors, and cyclin-dependent kinase inhibitors.

mTOR is a conserved checkpoint kinase that plays a pivotal role in the regulation cell of growth and proliferation. Rapamycin, also known as sirolimus, was first identified in 1975 as a product of a soil-dwelling bacterium on Rapa Nui, or Easter Island.[81] It acts by forming a complex with its intracellular receptor FK-binding protein (FKBP12), which then binds to the kinase domain of the mTOR complex and arrests cells in the G_1 (Gap 1) phase of mitosis. Although initially developed as an antibiotic, early work in the 1980s and 1990s demonstrated its antineoplastic properties.[82,83] mTOR inhibitors have been shown to inhibit the growth of leukemic cells, both in vitro and in vivo, in transgenic mice.[84,85] Sirolimus and other rapamycin analogs CCI-779 (temsirolimus) and RAD001 (everolimus) have shown antineoplastic effects in clinical trials[86] and have also been shown to be synergistic with traditional cytotoxic chemotherapy.[87] A pilot study to determine safety of sirolimus when administered with hyper-CVAD chemotherapy for ALL is ongoing at Thomas Jefferson University Hospital, and a phase I/II trial of RAD001 in

combination with chemotherapy in relapsed or refractory ALL is recruiting at MD Anderson Cancer Center.

Approximately 94% of B-lineage and 32% of T-lineage ALL express the FLT3 kinase.[88] Expression of both the kinase and mutations of the FLT3 gene can lead to constitutive activation of downstream elements (such as mitogen-activated protein kinase and AKT) and uncontrolled cellular proliferation. Two FLT3 inhibitors that have shown cytotoxicity in ALL are PKC412 (midostaurin)[89] and CEP701 (lestaurtinib).[90] Synergy has also been demonstrated with several chemotherapeutic agents including mitoxantrone and cytarabine.[91] Phase I/II clinical trials are underway in the pediatric population in ALL and the CALGB (trial 10603) is examining midostaurin in combination with chemotherapy in adult AML.

Flavopiridol (alvocidib, L86-8275) is a synthetic flavone derivative that inhibits the cyclin-dependent kinases involved in aberrant cell growth in leukemic cells. This compound binds to the adenosine triphosphate site of the cyclin-dependent kinases and leads to cell cycle arrest in $G_{0/1}$ and G_2, as well as inhibition of messenger RNA synthesis. This subsequently causes a depletion in antiapoptotic proteins such as B-cell lymphoma 2 and cyclin D1 and, theoretically explains increased apoptosis after exposure to flavopiridol.[92] In a phase I clinical trial combining flavopiridol and chemotherapy in refractory leukemia, approximately 50% of patients evidenced leukemia cytotoxicity by a $\geq$50% drop in blast counts and tumor lysis. Overall response rate was 31% in AML and 12.5% in ALL, with neutropenia as the major toxicity.[93] A second phase I trial also showed cytoreduction, but sustained response was uncommon. The dose-limiting toxicity was diarrhea.[94]

Other novel agents
NOTCH1
More than 50% of T-cell ALL is marked by a gain-of-function mutation in the NOTCH signaling pathway and constitutive activation.[95] The NOTCH inhibitor MK-0752 inhibits the cleavage of the NOTCH1 receptor, thus preventing the release of the intracellular domain and subsequently suppressing gene transcription. The resultant arrest of cells in $G_{0/1}$ increases apoptosis and decreases viability. A phase I trial led to minimal response in disease and dose-limiting diarrhea.[96] Alternate dosing and combination schemes are being investigated.

CXC chemokine receptor type 4
Stem cells are driven to "home" to the marrow microenvironment by an interaction between CXC chemokine receptor type 4 and stromal-derived factor alpha.[97] Interruption of this relationship has been utilized in the SCT arena, and the CXC chemokine receptor type 4 inhibitor plerixafor is now used as a mobilizing agent pre-transplant. Prevention of homing in ALL cells to the bone marrow niche can make them more accessible to treatment.[98]

Proteasome inhibitors
The ubiquitin-proteasome pathway is crucial for intracellular protein degradation. The proteasome is responsible for degrading damaged or misfolded proteins that have been labeled with a ubiquitin chain for destruction. Additionally this pathway is required for transcriptional regulation by mediating the activity of nuclear factor kappa B.[99] Nuclear factor kappa B is constitutively activated in some malignancies, making the proteasome pathway an attractive target to inhibit. Bortezomib (Velcade®) is currently used as a successful first-line treatment in multiple myeloma and is in trials for treatment of non-Hodgkin lymphomas. In ALL cells it has been shown to enhance the toxicity of typical induction chemotherapy.[100] A pediatric phase I trial of bortezomib in combination with chemotherapy has shown tolerance and efficacy,[101] and a number of phase I/II trials of bortezomib with other agents are underway in adults.

Conclusion
Advances in pediatric ALL over recent decades have led to improved cure rates. The adult population is in great need of similar advances and stands to benefit tremendously from the research discussed in this review. The challenges of sustainable remission and reduced morbidity and mortality in treatment remain to be surmounted. The aggressive efforts of current clinical trials that are investigating novel therapies both alone and with standard treatment offer hope for adults that is slowly beginning to be realized.

Disclosure
The authors report no conflicts of interest in this work.

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