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Novel Therapies for Relapsed Acute Lymphoblastic Leukemia

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Abstract

The outcome of salvage therapy for relapsed acute lymphoblastic leukemia (ALL) remains poor. Salvage therapy mimics regimens with activity in newly diagnosed ALL. Novel strategies under investigation as monotherapy or in combination with chemotherapy improve the treatment of relapsed disease. For some ALL subsets, specific therapies are indicated. The addition of targeted therapy in Philadelphia chromosome–positive ALL has improved responses in relapsed patients without resistance to available tyrosine kinase inhibitors. Nelarabine demonstrates activity as monotherapy in T-cell ALL and is approved by the US Food and Drug Administration. Clofarabine, a second-generation purine analogue approved in pediatric leukemia, has shown activity in adult acute leukemias including ALL and acute myeloid leukemia. The role of pegaspargase in adult ALL requires further investigation. The benefit of matched related-donor allogeneic stem cell transplantation is significant for standard-risk ALL but not for high-risk ALL. Development of new drugs and agents tailored to subset-specific cytogenetic-molecular characteristics remains vital to success in treating adult ALL.

Introduction

Acute lymphoblastic leukemia (ALL) refers to a group of lymphoid disorders resulting from monoclonal pro-liferation and expansion of lymphoid blasts in the bone marrow, blood, and other organs. ALL is the most common childhood acute leukemia, accounting for about 80% of childhood leukemias, but it comprises only 20% of adult leukemias. ALL occurs at a rate of approximately 1 to 1.5 per 100,000 persons and exhibits a bimodal age distribution, with an early peak in children 4 to 5 years old (4 to 5 per 100,000), followed by a second peak at about 50 years of age (2 per 100,000) [1]. ALL is relatively uncommon in late childhood, adolescence, and young adulthood. Advances in ALL therapy have led to long-term survival rates exceeding 80% in children. Complete remission rates comparable to those in children can be achieved in adults by adapting pediatric ALL treatment strategies, but only about 30% to 40% of adults achieve long-term disease-free survival (DFS). Better understanding of the biology of ALL has led to changes of the pathologic classification of the disease, emergence of new treatment options, and institution of risk-adapted therapies. New therapies are emerging based on the definition of specific cytogenetic-molecular abnormalities. However, long-term survival of adults is still inferior to that of children. Development of

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new drugs and agents tailored to subset-specific cytogenetic-molecular characteristics remains vital to therapeutic success in adult ALL.

Etiology

The etiology of ALL remains unknown. Chromosomal translocations occurring in utero during fetal hematopoiesis have been suggested as the primary cause of pediatric ALL, and postnatal genetic events are suggested as secondary contributors. A higher incidence of ALL is noted among monozygotic and dizygotic twins of patients with ALL, reflecting possible genetic predisposition. Patients with trisomy 21, Klinefelter's syndrome, and inherited diseases with excessive chromosomal fragility (eg, Fanconi's anemia, Bloom syndrome, and ataxia-telangiectasia) have a higher risk of developing ALL [2]. Implications have also hinted at infectious etiologies. Associations between human T-cell lymphotrophic virus type 1 and adult T-cell leukemia/lymphoma, as well as HIV and lymphoproliferative disorders, have been established. In addition, associations with varicella and influenza viruses have been suggested.

Classification

The French-American-British (FAB) Cooperative Group distinguishes three ALL groups (L1 to L3) based on morphologic criteria (cell size, cytoplasm, nucleoli, basophilia, vacuolation) [3]. The morphologic distinction between L1 and L2 has lost its prognostic significance. L3 morphology is associated with mature B-cell ALL (Burkitt's leukemia). The World Health Organization (WHO) proposed new guidelines for the diagnosis of neoplastic diseases of hematopoietic and lymphoid tissues [4,5]. In addition to lowering the blast count to greater than or equal to 20% as sufficient for an ALL diagnosis, the morphologic distinction of L1, L2, and L3 morphologies is abandoned as no longer relevant. Both the FAB and WHO classification systems continue to rely heavily on morphologic assessment. Identification of the immunophenotype has become a major part of ALL diagnosis. Three broad groups can be distinguished: precursor B-cell ALL, mature B-cell ALL, and T-cell ALL.

Prognostic Factors

Several factors are considered when determining prognosis for adult patients with ALL. The presence of these risk factors increases the risk of relapse. Older age, high leukocyte count, immunophenotype other than T-cell, Philadelphia chromosome (Ph) positivity, and longer time to achieve initial complete response (CR) have all been associated with poor prognosis [6]. Other predictors of poor prognosis that have been suggested include poor performance status, presence of organomegaly, low platelet counts, low albumin levels, and elevated serum lactate dehydrogenase levels. In relapsed ALL, the presence of circulating peripheral blasts at the initiation of salvage treatment correlates with lower likelihood of response to chemotherapy and shorter survival [6]. In addition, short duration of complete response, increased bone marrow blasts, thrombocytopenia, and hypoalbuminemia adversely affect survival in relapsed patients [7••].

Chemotherapy

The treatment of ALL remains among the most complex therapies of anticancer programs. Multiple drugs are molded into regimen-specific sequences of dose intensity and time intensity, with the goal of reconstituting normal hematopoiesis, preventing the emergence of resistant subclones, providing adequate prophylaxis of sanctuary sites (eg, central nervous system [CNS], testicles), and eliminating minimal residual disease (MRD) through postremission consolidation and maintenance [2]. Three distinct phases (induction, intensified consolidation, and maintenance) are distinguished, with four components including CNS prophylaxis, which accompanies induction and consolidation.

The combination of vincristine, corticosteroids, and anthracyclines represents the backbone of ALL induction regimens. This combination achieves remission rates of 72% to 92%, with a median remission duration of about 18 months [8]. Dexamethasone is often substituted for prednisone because of better in vitro antileukemic activity and achievement of higher drug levels in the cerebrospinal fluid (CSF) [9,10]. Although L-asparaginase is an important agent in the treatment of pediatric ALL, its role in adult ALL is not well defined. Hematopoietic growth factors during induction accelerate recovery from myelosuppression and allow timely administration of dose-intense treatment regimens [11].

Consolidation represents a repetition of a modified induction schedule, rotational consolidation programs, or stem cell transplantation. Novel strategies try to emphasize subtype-oriented or risk-oriented approaches of consolidation programs.

The mainstays of maintenance therapy are daily 6-mercaptopurine, weekly methotrexate, and monthly pulses of vincristine and prednisone, given over 2 to 3 years. Extension of maintenance beyond 3 years is not beneficial, nor is the omission or shortening of therapy [2]. No maintenance therapy is given in mature B-cell ALL, as these patients have a high cure rate with short-term, dose-intense regimens, and relapses beyond the first year in remission are rare. The best maintenance for patients with Ph-positive ALL remains disputed but should incorporate effective BCR-ABL tyrosine kinase inhibitors.

Although CNS disease is found in less than 10% of patients at diagnosis, the rate can increase to as high as 50% to 75% at 1 year without CNS-directed therapy [12–14]. Standard prophylaxis for CNS malignancy can involve radiation therapy, systemic chemotherapy, intrathecal (IT) chemotherapy, or a combination of these. Cranial irradiation is associated with adverse effects such as secondary neoplasms, endocrinopathy, neurocognitive dysfunction, and neurotoxicity [15–17]. Combining early intensive systemic and IT chemotherapy can lower the CNS relapse rate in patients with ALL and may provide the opportunity to omit prophylactic cranial irradiation [18]. High-dose cytarabine (1–7.5 mg/m^2) and methotrexate (5–8 g/m^2) have the ability to penetrate the blood–brain barrier and can serve as CNS prophylaxis [19–22]. However, it is difficult to maintain prolonged therapeutic concentrations of drug in the CSF using only systemic chemotherapy. Furthermore, systemic therapy is associated with wide-spread toxicities. High-dose cytarabine is associated with liver dysfunction, cerebellar dysfunction, mucositis, diarrhea, rash, and fever [23]. High-dose methotrexate is associated with renal dysfunction, transient

hepatitis, mucositis, and (rarely) neurotoxicity [24]. The inclusion of IT chemotherapy in CNS prophylaxis protocols aims to improve the efficacy of systemic therapy while circumventing its limitations. IT chemotherapy allows direct intra-CSF treatment and potentially sustained therapeutic drug concentration in the CSF [13]. Commonly used IT therapies include methotrexate, cytarabine, liposomal cytarabine, and thiotepa. In the absence of IT therapy, isolated CNS recurrence can account for 10% to 16% of relapses, warranting the inclusion of IT chemotherapy in CNS prophylactic regimens [24]. The efficacy of high-dose methotrexate, cytarabine, and IT cytarabine in preventing CNS relapse was demonstrated by comparing a regimen with no CNS prophylaxis (preceding a VAD [vincristine-doxorubicin-dexamethasone] ALL treatment regimen) with a series of modified VAD regimens that included different prophylactic modalities in adult patients treated with four consecutive protocols [13]. CNS relapse was reduced in those patients who received systemic or IT CNS prophylaxis along with VAD, modified VAD, or hyper-cyclophosphamide VAD (hyper-CVAD), compared with those not receiving prophylaxis. More recently, the use of IT chemotherapy in combination with the hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin and dexamethasone, alternating with methotrexate and high-dose cytarabine) reduced the incidence of CNS relapse to 4% [12]. The number of IT injections depends on the risk of CNS relapse (two IT treatments per course). Mature B-cell ALL, serum lactate dehydrogenase levels, and a high proportion of bone marrow cells in a proliferative state (≥ 14% of cells in $S+G_2M$ phase of the cell cycle) have been associated with a higher risk of CNS disease in adults [25]. Commonly, patients at low risk of CNS disease receive four IT treatments, those with unknown risk receive eight, and those with high risk of disease, including all patients with mature B-cell ALL, receive 16 IT treatments [26].

Minimal Residual Disease in Adult ALL

MRD describes the presence of disease below the threshold of detection by conventional methods (light microscopy and cytochemical stains). Different methods are available to detect and monitor MRD, including fluorescence in situ hybridization (FISH), multicolor flow cytometry, and polymerase chain reaction (PCR) assays, especially real-time quantitative (RQ) PCR. Multicolor flow cytometry and PCR techniques take advantage of either fusion transcripts resulting from chromosome abnormalities (eg, *BCR-ABL*, *MLL-AF4*, *TEL-AML1*) or patient-specific junctional regions of rearranged immunoglobulin and T-cell receptor genes [2].

Measurement of MRD in ALL has become increasingly important for assessing risk of relapse. The extent to which MRD needs to be controlled or eliminated remains uncertain. Several questions remain:

- What are the most appropriate time points for measurement of MRD? Persistence of MRD early in CR typically does not have the same significance as its detection in later stages of therapy.
- Is there a definable threshold of residual disease by quantitative assays that would predict high relapse probability?

- Is it necessary to revise response criteria and introduce the concept of a “molecular relapse”? It should be emphasized that molecular relapse does not always predict clinical relapse, and intensification of therapy under these circumstances may not be appropriate.
- Can quantitation of MRD over time lead to a new risk classification with impact on choice of consolidation and maintenance strategies?

Most of our current knowledge about MRD and its kinetics derives from studies in childhood ALL and differences in pattern and dynamics of clearance of MRD between adult and childhood ALL. Marrow samples from 33 adults and 21 children were analyzed by PCR for immunoglobulin heavy-chain gene rearrangements at specific time points after diagnosis [27]. Among patients who remained in remission, a decrease in MRD positivity occurred during the first 12 months. The proportion of positive tests decreased faster in children than in adults, suggesting more rapid resolution of MRD, particularly in the first 6 months of CR.

Disease Subtype–Specific Approaches

Philadelphia chromosome–positive ALL

Ph positivity is the most common cytogenetic abnormality in adults with ALL, occurring in 20% to 30% of patients. With conventional chemotherapy, the outcome of patients with Ph-positive ALL is poor, with long-term DFS rates less than 10% [2]. Allogeneic stem cell transplantation (SCT) is therefore recommended for all patients with Ph-positive ALL who achieve CR. Incorporation of targeted therapy using tyrosine kinase inhibitors such as imatinib mesylate has altered the outcome of this ALL subset. Synergistic effects are possible with the addition of tyrosine kinase inhibitors to chemotherapy including anthracyclines, vincristine, and cytarabine. Although the optimal schedule of tyrosine kinase inhibitors has yet to be determined in ALL, early initiation and prolonged treatment courses appear to provide the best outcomes. Imatinib has shown encouraging results in Ph-positive ALL, with CR rates of 96% [28,29]. DFS at 2 years was 87% with the combination of hyper-CVAD and imatinib versus 28% with hyper-CVAD alone in this group of patients. Similar results have been reported in other studies of imatinib and dose-intense chemotherapy programs. The role of second-generation tyrosine kinase inhibitors in ALL is under investigation. The dual *src* and ABL inhibitor dasatinib has clinical activity in patients with imatinib-resistant chronic myeloid leukemia (CML) and Ph-positive ALL. In 28 patients with newly diagnosed Ph-positive ALL, the addition of dasatinib to hyper-CVAD resulted in 93% CR, with 50% of patients achieving complete molecular remission and 18% obtaining a major molecular response at a median of 10 weeks from initiation of therapy [30]. MRD was negative in 85% of patients at a median of 3 weeks. However, 18% of patients relapsed, and four developed new ABL mutations (T315I, F359V), confirming the need for agents that overcome resistance to available tyrosine kinase inhibitors.

Burkitt’s 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 DFS rates of 60% to 80%. Relapses are rare after the first year in remission. Intensive early

prophylactic IT therapy (with or without cranial irradiation), in addition to intensive systemic administration of cytarabine and methotrexate, reduces the CNS relapse rate [2].

Expression of CD20 is detected in 35% of patients with adult ALL and has been associated with a worse prognosis. Expression is higher in ALL subsets: up to 55% in Ph-positive ALL and almost ubiquitous in mature B-cell ALL. Of 23 evaluable patients with non–HIV-related mature-B ALL treated with the combination of hyper-CVAD and rituximab, 91% achieved CR [31,32]. Compared with a historical control of 48 patients treated with hyper-CVAD alone, the 2-year rates for survival were superior for the hyper-CVAD plus rituximab combination (89% vs 58%, $P < 0.001$), especially for those patients over 60 years of age (89% vs 19%, $P < 0.01$).

T-cell ALL

Current therapies for T-cell ALL produce high rates of response, but about half of patients will relapse within 2 years. Nelarabine demonstrates antineoplastic activity in patients with relapsed/refractory T-cell ALL. Nelarabine produced CR rates of 31% with minimal toxicities in relapsed/refractory ALL patients [33]. Studies evaluating nelarabine as a front-line therapy in combination with hyper-CVAD for newly diagnosed T-cell ALL are ongoing.

ALL in elderly patients

Elderly patients (defined as older than 60 or 65 years) have a poorer prognosis than younger patients when treated with similar regimens, and long-term survival rates remain low [34•]. Regimens must be designed for age-specific factors such as organ function and performance status, as well as for causes of treatment failures. Use of the hyper-CVAD regimen in these patients has decreased the incidence of resistant disease when compared with earlier regimens (27% vs 5%, $P < 0.001$) [34•]. However, the primary cause of failure in elderly patients has now shifted from resistant disease to complications associated with myelosuppression. The induction mortality rate was 12% for elderly patients treated with the hyper-CVAD regimen. However, administering induction therapy in a high-efficiency particulate air–filtered room (protected environment) reduced mortality to 5%. Treatment failure and disease recurrence must be considered if reduction in dose intensity is to be used as a possible strategy to improve outcomes in this patient population. Novel agents, as well as less toxic versions of older agents, should be investigated in the elderly population. Furthermore, induction therapy in a protected environment should be considered for patients over 60 years of age to minimize mortality.

Salvage Therapy

The outcome of salvage therapy in adult ALL remains poor. CR rates rarely exceed 50%, and long-term DFS is rare. Independent prognostic factors associated with achieving CR include duration of first CR and platelet count [7••]. Short duration of first CR, thrombocytopenia, elevated percentage of bone marrow blasts, and low albumin level are associated with poor survival rates (Table 1). The survival of relapsed patients decreases in association with the number of adverse prognostic factors. In patients undergoing second salvage therapy, the estimated 12-month survival rates were 33% for patients with 0 or 1

risk factor, 14% with 2, 8% with 3, and 0% with 4 risk factors [7••]. Salvage regimens are structured according to outcomes from front-line therapy. Newer agents have been approved in the relapsed setting, and the role of novel formulations of conventional active agents are being further investigated (Table 2).

Clofarabine

Clofarabine is a second-generation purine nucleoside analogue with activity in acute leukemias. In phase 2 trials of clofarabine in relapsed or refractory pediatric leukemias, 31% of patients with ALL responded, including 12% CR, 8% complete response without platelet recovery (CRp), and 10% partial response [35]. Based on the response rate in pediatric relapsed ALL, the US Food and Drug Administration approved clofarabine for this indication. The activity of clofarabine has also been demonstrated in adult acute myeloid leukemia, myelodysplastic syndrome, and CML in blast phase [36,37]. The maximum tolerated dose (MTD) in adults with leukemia is 40 mg/m^2 per day for 5 days, 20 times the MTD studied in solid tumors [38]. Unlike other purine analogues, clofarabine is not associated with neurotoxicity. Hepatotoxicity, skin rashes, drug fever, and palmoplantar erythrodysesthesia have been reported [35–38]. Studies exploring combinations of clofarabine with known active agents for ALL are ongoing.

Nelarabine

Nelarabine, an araguanosine analogue, has been shown to be very active as a single agent in recurrent T-cell ALL, with a response rate more than 50% in first bone marrow relapse. When administered on an alternate-day schedule of 1.5 mg/m^2 per day (days 1, 3, and 5) in relapsed/refractory T-cell ALL, 31% of patients achieved CR [33]. The median DFS and overall survival was 20 weeks. Neurotoxicity with nelarabine has been of concern since initial studies. At the recommended dose, neurotoxicity was reported in 37% of patients, with all events being grade 1 or 2. However, previous treatment with chemotherapy regimens that may have included vincristine, methotrexate, cytarabine, and IT chemotherapy may have contributed to the occurrence of neurotoxicity. Patients studied were not treated with concurrent intrathecal chemotherapy; concurrent use of IT chemotherapy and nelarabine may compound the risk of neurotoxicity, so caution is advised. Nelarabine in combination with hyper-CVAD is currently under investigation in newly diagnosed T-cell ALL. Giving nelarabine at a dosage of 650 mg/m^2 daily for 5 days every 28 days for two courses as consolidation following completion of the hyper-CVAD sequence has been found to be feasible, but its true impact on survival has yet to be determined [39].

Sphingosomal vincristine

Vincristine, a key component in ALL therapy, causes peripheral neuropathy requiring dose reductions or omission from the chemotherapy regimens. Liposomal formulations of chemotherapeutic agents generally produce less toxicity and greater efficacy. Sphingosomal vincristine may serve as a replacement for conventional forms of vincristine. With the use of sphingosomal vincristine, activity has been observed in relapsed ALL and neurotoxicity has been minimal when compared with the conventional formulation [40]. Though capping doses of conventional vincristine at 2 mg has become common practice, sphingosomal vincristine may be administered without dose capping [41•]. The MTD was 2.25 mg/m^2

weekly when given in combination with dexamethasone (40 mg/d on days 1 through 4 and 11 through 14 of each 28-day cycle) in relapsed or refractory ALL; 19% CR was achieved [42]. Preliminary results are encouraging, with further studies planned to evaluate sphingosomal vincristine given weekly as single-agent therapy [41•].

Pegaspargase

The role of pegaspargase (*Escherichia coli* asparaginase linked to polyethylene glycol) in adult ALL requires further exploration. Asparaginase represents a key component of pediatric ALL regimens. Although critical to DNA and RNA synthesis, asparagine cannot be produced by ALL cells, and its depletion through breakdown by asparaginase results in the death of leukemic cells. Applying variations of pediatric regimens to adults creates concern regarding toxicities with asparaginase. Pegaspargase minimizes reactions while maintaining the enzymatic activity of asparaginase. The efficacy of pegaspargase appears to be dose-dependent [43]. Induction therapy with dexamethasone, daunorubicin, IT methotrexate, and 1000 U/m^2 of pegaspargase produced a CR rate (91%) similar to the rate (90%) produced with the use of 2000 U/m^2. However, there was a trend toward earlier and higher molecular CR with the escalated dose. The impact of this difference on survival is unknown. When pegaspargase was substituted for L-asparaginase in the Berlin-Frankfurt-Münster (BFM) regimen (prednisone, vincristine, daunorubicin, and L-asparaginase followed by cyclophosphamide, cytarabine, mercaptopurine, and IT methotrexate), 96% CR was reported [44,45].

Augmented hyper-CVAD

Modifications to the hyper-CVAD regimen mimicking approaches from pediatric regimens improve the outcomes in relapsed or refractory ALL in adults. The design of the “augmented” hyper-CVAD regimen intensifies the dosages of vincristine and dexamethasone and adds L-asparaginase. With each course of “augmented” hyper-CVAD, vincristine dosed at 2 mg and L-aspara-ginase dosed at 20,000 units were administered on days 1, 8, and 15 [46,47••]. Additionally, dexamethasone was increased from the standard hyper-CVAD regimen to 80 mg/d on days 1 through 4 and days 15 through 18. Of 49 patients treated, 45% achieved CR, with a median remission duration of 4.75 months [47••]. Toxicities related to L-asparaginase were frequent, with 5% of patients removed from the study because of intolerance. The role of pegaspargase in combination with this regimen is currently being investigated.

Sequencing of medications

Specific sequencing of medications enhances antileukemic effect. For example, asparaginase increases the sensitivity of leukemic cells to methotrexate, and administering it 24 hours after methotrexate reduces methotrexate’s toxicity [48]. In patients with previously treated ALL, combining sequential moderate-dose methotrexate (100–225 mg/m^2) and asparaginase with vincristine and dexamethasone (MOAD) proved beneficial in attaining remission. CR was achieved in 11 (79%) of 14 previously treated patients. The median duration of CR was 7.5 months and the median survival was 11.2 months. Systemic anaphylaxis should be of concern when using asparaginase products, but it can be managed by antihistamines,

epinephrine, or both. The use of intramuscular versus intravenous administration to minimize allergic reactions has also been considered.

Tyrosine kinase inhibitors

SCT is recommended for all patients with Ph-positive ALL in first CR. For patients not eligible for transplantation, survival is minimal. Acquired resistance to the tyrosine kinase inhibitor imatinib results from mutations in the kinase domain of ABL and BCR-ABL amplification. Second-generation tyrosine kinase inhibitors appear promising in the management of imatinib-resistant ALL. Though imatinib binds to BCR-ABL only in the closed conformation, dasatinib binds in both the open and closed conformations, increasing its affinity to BCR-ABL. The ability of dasatinib to inhibit *src* activity may provide an advantage over imatinib by blocking BCR-ABL activity through a separate mechanism. Dasatinib, in combination with chemotherapy (hyper-CVAD), was evaluated in 14 patients with relapsed Ph-positive ALL or CML with lymphoid blast crisis [49••]; 71% of the patients achieved CR and 29% attained CRp. Major molecular response was achieved in 64%. Of four patients who had relapsed, two acquired the T315I mutation, resistant to currently available tyrosine kinase inhibitors.

Stem Cell Transplantation

Although SCT is superior to chemotherapy, with long-term DFS rates of 20% to 40% in salvage, only 30% to 40% of patients who achieve a second CR are eligible for SCT, and fewer than half have enough time before relapse to undergo SCT. Considering a DFS rate of about 25%, only a fraction of the total population at risk would thus benefit from transplantation. The outcome with SCT versus continuation of chemotherapy in ALL has been debated. Traditionally, SCT has been reserved for patients with Ph-positive ALL or in patients considered high-risk (age > 35 years, B lineage with white blood cell count $\geq 100 \times 10^9$/L, T lineage with white blood cell count $\geq 30 \times 10^9$/L) [50••]. In high-risk patients, survival at 5 years was not significantly different between patients treated with matched related-donor SCT and those treated with continued chemotherapy or autologous SCT. However, in patients not considered high-risk, improvements in survival at 5 years were significantly greater in patients treated with matched related-donor SCT. In both risk groups, allogeneic SCT produced a lower rate of relapse than chemotherapy or autologous SCT. For patients without a suitable donor, chemotherapy is favored rather than autologous SCT.

Conclusions

Progress in the understanding of the biology and patho-genesis of adult ALL has helped improve outcome and prognosis, yet advances have been minimal in comparison with other malignancies. More intensive regimens combined with targeted therapy are being evaluated with encouraging results. Targeted therapy in addition to chemotherapy proves beneficial in CD20-positive disease and Ph-positive ALL. CNS prophylaxis remains a cornerstone of ALL therapy, and can be carried out safely and effectively with a combination of IT and high-dose systemic chemotherapy. Allogeneic SCT is beneficial in first remission for all risk subtypes of ALL. Autologous SCT is inferior to consolidation chemotherapy in patients without a sibling donor.

As in other leukemias, the key to further improving the prognosis of adult ALL lies in an appreciation and recognition of the heterogeneity of ALL, which should be understood as many disease states, not just one or a handful. Increasing appreciation of the biologic characteristics of ALL subsets will lead to more elaborate risk-oriented treatment programs. Novel strategies under investigation as monotherapy or in combination with chemotherapy improve the treatment of relapsed disease. Treatment regimens in ALL have historically been complex and may continue to be so. Development of new drugs and agents tailored to subset-specific cytogenetic-molecular characteristics remains vital to success in treating adult ALL.

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Table 1

Prognostic factors in relapsed acute lymphoblastic leukemia

Poor prognostic factors for CR
Albumin level < 3 g/L*
Duration of first CR < 36 months*
Hemoglobin level < 10 g/dL
Platelet count ≤ 50 × 10^9/L*
Bone marrow blasts > 50%
Peripheral blood blasts ≥ 1%
Poor prognostic factors for survival
Albumin level < 3 g/L*
Duration of first CR < 36 months*
Hemoglobin level < 10 g/dL
Platelet count ≤ 50 × 10^9/L*
Bone marrow blasts > 50%*
Peripheral blood blasts ≥ 1%
White blood cell count > 20 × 10^9/L

CR—complete response.

(*Adapted from* O'Brien et al. [7••].)

*Independent prognostic factors identified by multivariate analysis. All prognostic factors listed significantly reduced the rate of CR and survival.

Table 2

New therapies for relapsed acute lymphoblastic leukemia

Investigational therapy	Pharmacologic classificatic	Indication	Stage of development	Overall response rate	Adverse effects
Clofarabine [36–38]	Nucleoside analogue	ALL/AML	FDA-approved in pediatric ALL; phase 2 (adults)	13%	Hepatotoxicity, rash, drug fever, palmoplantar erythrodysesthesia
Hyper-CVAD + dasatinib* [49••]	Chemotherapy + tyrosine kinase inhibitor	Philadelphia chromo-some–positive ALL	Phase 2	100% in combination with chemotherapy	Bleeding, pleural and pericardial effusion, liver dysfunction
Sphingosomal vincristine [40,41•,42]	Liposome-encapsulated vinca alkaloid	ALL	Phase 2	14%	Peripheral neuropathy, orthostasis, headache
Nelarabine [33]	Nucleoside analogue	T-cell ALL	FDA-approved	41%	Peripheral sensory neuropathy, seizure, fatigue, muscle weakness, gastrointestinal distress
Pegaspargase* [44,45]	Pegylated asparaginase	ALL	FDA-approved in pediatric ALL	96% in combination with chemotherapy	Hypersensitivity reactions, liver dysfunction, hyperglycemia, coagulation factor abnormalities, pancreatitis, cerebral dysfunction

ALL—acute lymphoblastic leukemia; AML—acute myelogenous leukemia; FDA—US Food and Drug Administration; hyper-CVAD—vincristine, doxorubicin, and dexamethasone with hyper-cyclophosphamide.

* Responses reported in combination with chemotherapy.