Published in final edited form as:
Clin Lymphoma Myeloma. 2009 ; 9(Suppl 3): S222. doi:10.3816/CLM.2009.s.016.

High-Risk Childhood Acute Lymphoblastic Leukemia

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Abstract

Although most children with acute lymphoblastic leukemia (ALL) are cured, certain subsets have a high risk of relapse. Relapse risk can be predicted by early response to therapy, clinical and pharmacogenetic features of the host, and genetic characteristics of leukemic cells. Though early treatment response can be assessed by the peripheral blast cell count after 1 week of single-agent glucocorticoid treatment or percent of bone marrow blasts by morphology after 1 or 2 weeks of multiagent induction treatment, determination of minimal residual disease by polymerase chain reaction (PCR) or flow cytometry after 2 to 6 weeks of induction is the most precise and useful measure. Augmented therapy has improved outcome for the poor responders to initial treatment. Infants with mixed-lineage leukemia (MLL)–rearranged ALL comprise a very poor-risk group wherein further intensification of chemotherapy causes significant toxicity. Hybrid protocols incorporating drugs effective for acute myeloid leukemia could improve survival, a strategy being tested in international trials. Studies on the biology of MLL-induced leukemogenesis have prompted the development of novel targeted agents, currently under evaluation in clinical trials. Short-term outcomes of patients with Philadelphia chromosome (Ph)–positive ALL have improved significantly by adding tyrosine kinase inhibitors to standard chemotherapy regimens. New agents and methods to overcome resistance are under investigation, and allogeneic stem cell transplantation is recommended for certain subsets of patients, for example those with Ph^+ and T-cell ALL with poor early response. Genome-wide interrogation of leukemic cell genetic abnormalities and germline genetic variations promise to identify new molecular targets for therapy.

Keywords

Childhood cancer; Dasatinib; Imatinib; Infant ALL; Pediatric disease; Philadelphia chromosome; positive disease; Slow early response

Introduction

More than 80% of children diagnosed with acute lymphoblastic leukemia (ALL) can be cured with current multiagent regimens, but subsets of patients have significantly worse outcomes.[1,2] In this review, we identify patients with high-risk ALL, summarize their management, and highlight ongoing research to improve outcome. Novel therapies, the ability to intensify therapy while providing enhanced supportive care, and increased access to sources of stem cells for

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Disclosures

Dr. Ching-Hon Pui has served as a paid consultant for McKinney's & Company, and has received Honorarium from sanofiaventis U.S. The authors report no other relevant potential conflicts of interest.

transplantation have provided effective means to increase cure rates for patients with high-risk ALL.

Study groups worldwide use varying criteria to select patients for intensified therapy in first remission (Table 1).[3–13] Risk stratification has evolved from defining 2 risk groups (high vs. standard) to the current classification system with 4 groups defined by the Children's Oncology Group (COG): low-risk, standard-risk, high-risk, and very-high-risk.[14] The COG risk groups were devised after assessing clinical and cytogenetic data from more than 6000 patients enrolled on previous studies. The estimated 4-year event-free survival (EFS) for these 4 groups is 91%, 86%, 76%, and 46%, respectively.[3] Certain subsets of patients, such as those with Philadelphia chromosome (Ph)–positive or infant ALL, have always been considered high-risk; however, with improved insights into molecular defects and precise minimal residual disease (MRD) measurements, it is possible that some high or very-high-risk patients will be reclassified as standard-risk. For example, a child younger than 10 years old with Ph^+ ALL presenting with a low white blood cell (WBC) count and a good response to remission induction chemotherapy or an infant older than 6 months without *MLL* gene rearrangement in leukemic cells might have a relatively good prognosis with modern risk-directed therapy.

Slow Early Responders

It is well established that initial response to the first few weeks of remission induction chemotherapy predicts long-term disease-free survival (DFS) in ALL.[15] Although the precise biologic factors contributing to early response have not entirely been defined, rapid disease regression in the initial phase of therapy is the result of a dynamic interplay of the chemosensitivity of the leukemic cells, effectiveness of the treatment regimen, and host pharmacogenetics.

Defining and Quantifying Early Response

Methods of quantifying early response have become increasingly sensitive, objective, and precise. The Berlin-Frankfurt-Münster (BFM) group has traditionally used the peripheral blood blast count after a 7-day prednisone prephase to classify patients as prednisone-good responders (< 1000/μL blasts on day 8) or prednisone-poor responders (> 1000/μL blasts).[16] In the ALL-BFM-90 trial, 10% of all patients were prednisone poor responders and a had a 6-year EFS of only 34% compared with 82% for those with a good response.[17] Outcome was poor for patients with a poor prednisone response even within clinically or cytogenetically defined subsets who would otherwise have had a good prognosis. This simple method of assessing early response has stood the test of time and is preferred by many developing countries for its ease of implementation. Morphologic assessment of a bone marrow aspirate at various time points during remission induction such as day 7, 15, or 22 or at the end of induction (4–8 weeks) has also been used to quantify response.[18,19] A good response is represented by a M1 marrow (< 5% blasts) with trilineage hematopoiesis, but even blast counts of 1%–4% at day 7 or 22 heralded a poor prognosis in St. Jude Total Therapy Studies XI and XII.[19] Thus, the development of highly sensitive tools to detect MRD, such as polymerase chain reaction (PCR) for antigen receptor rearrangements or fusion transcripts or immunologic detection of blasts by flow cytometry, allows closer monitoring of the kinetics of response in patients thought to be in morphologic remission.[20–22] Polymerase chain reaction is approximately a log more sensitive than flow cytometry, but both methods are highly concordant.[23] The BFM group measures MRD by PCR at 2 time points: after induction and after consolidation. Patients are classified based on their MRD response as MRD-standard-risk, MRD-intermediate-risk, or MRD-high-risk. The updated 10-year EFS corresponding to these 3 MRD-based groups is 93%, 74%, and 16%, respectively.[24] At St. Jude, MRD is measured by flow cytometry in virtually all patients and by PCR in a very small subset wherein a suitable leukemia-associated immunophenotype is not identified at diagnosis (approximately

2% of patients); a poor response is defined as MRD of > 1% at day 15 or > 0.01% at the end of induction.[21] MRD is also prognostically relevant for children undergoing hematopoietic stem cell transplantation (HSCT)[25] and for monitoring response following retrieval therapies for relapse.[26] The practical aspects of MRD monitoring in large multi-institutional trials are being optimized.[22,24] In addition, a simple and inexpensive flow cytometry–based technique that uses only 3 antibodies has proven informative for risk stratification.[27]

Augmenting Therapy for Slow Early Responders

Although the definition of early response and the optimal time points for measurement are debatable, augmentation of subsequent therapy for patients who demonstrate a slow early response can significantly improve cure rates. Extended induction and consolidation are used to deepen morphologic remission.[28,29] Early postinduction augmentation by increased intensity of relatively nonmyelosuppressive therapy (eg, glucocorticoid, asparaginase, and vincristine) without interruption of treatment improved the 5-year EFS from 55% to 75% in a randomized COG study of 340 patients with a slow early response (defined as > 25% bone marrow blasts at day 7 but < 5% blasts by day 28).[29] Although the reduced treatment intensity used in the ALL-BFM-90 trial did not decrease EFS for patients with a good prednisone response, decreased intensity of treatment, especially that of alkylating agents in ALL-BFM-90 as compared with ALL-BFM-86 led to inferior outcomes for patients with a poor prednisone response.[17] The 6-year EFS for poor responders to prednisone decreased from 46% in ALL-BFM-86 to 34% in ALL-BFM-90. Subsequently, in ALL-BFM-95, reintroducing alkylating agents and a reinduction block improved the 6-year EFS to 55% for patients with a poor prednisone response.[4] The Italian AEIOP-95 study repeated the same BFM reinduction block twice and achieved a 4-year EFS of 61.1% in patients with a poor prednisone response.[5]

Early incorporation of novel agents into front-line trials for high-risk patients is another approach to improving outcome. Nelarabine, a purine nucleoside analogue, is a promising agent with activity in relapsed T-cell malignancies and has been granted FDA approval for patients with relapsed or refractory T-cell ALL or lymphoblastic lymphoma.[30] Neurotoxicity was dose limiting in phase I/II trials. A COG pilot study tested the feasibility and safety of nelarabine in combination with intensive BFM therapy[31] and in the current protocol for newly diagnosed T-cell ALL (AALL0434; NCT00408005), patients with slow early response (M2 marrow or MRD ≥ 1% at the end of remission induction) are randomly assigned to treatment arms of augmented BFM therapy with or without nelarabine.

As demonstrated by the studies described previously, postinduction intensification improves the outcome of patients with a slow early response to therapy. The ability to monitor MRD at earlier time points (eg, day 15) allows even earlier intensification for patients with suboptimal responses. At St. Jude, therapy is intensified during the second part of remission induction for patients with 1% or greater MRD at day 15 by administering an extra dose of PEG-asparaginase. Patients with MRD levels of 5% or more at the same time point also receive fractionated cyclophosphamide to increase the probability of blast clearance by the time induction is completed.

Management of Remission Induction Failure

Induction failures (defined as > 5% blasts at the end of induction) might be considered an extreme form of slow response. In the FRALLE-93 study, approximately 80% of patients with induction failures achieved complete remission with the following salvage therapies: CAZED (dexamethasone, cytarabine, cyclophosphamide, etoposide, idarubicin, daunomycin, intrathecal therapy), VANDA (dexamethasone, high-dose cytarabine, mitoxantrone, etoposide, asparaginase, intrathecal therapy), or the R3 regimen (dexamethasone, high-dose cytarabine, etoposide, intrathecal therapy).[32] Although 80% of patients subsequently achieved

complete remission, only 30% were long-term survivors, emphasizing the importance of early response. In the recent COG study AALL0031 for very-high risk ALL, 21 of 22 patients with induction failure achieved complete remission after 2 additional intensive chemotherapy cycles.[33] Though longer follow-up data is awaited, the 2-year EFS for 12 patients who continued to receive chemotherapy was 46% versus 67% for 9 patients who subsequently underwent transplantation. At St. Jude, patients with induction failure are given consolidation and reintensification therapy, followed by allogeneic HSCT when they achieve complete remission, preferably with negative MRD.

Biologic Factors Influencing Early Response

Slow response to current risk-adapted front-line therapy can be circumvented by intensification including transplantation in a subset of patients, but a third of patients require novel strategies.[29,34] Insights into the biologic basis of inferior response are necessary. Individual host response to chemotherapeutic agents is influenced by genetic polymorphisms in drug transporters and metabolizing enzymes.[35,36] A candidate gene approach identified that a common polymorphism in the *CCR5* gene (+246 A > G) is linked to MRD response.[37] Genome-wide scans of germline single-nucleotide polymorphism (SNP) variations in children with ALL have identified multiple SNPs significantly associated with MRD at the end of induction.[38] A notable proportion of SNP genotypes that were associated with high residual disease correlated well with decreased drug exposure, either by increased clearance of etoposide and methotrexate or lower accumulation of methotrexate polyglutamates. This study underscores the contribution of individual host factors that play a role in response to therapy. In addition, global gene expression signatures of leukemic blasts identified at diagnosis can help predict MRD response, and, indirectly, long-term outcome.[39,40] Dissecting the pathways represented by these differentially expressed genes might identify candidate targets for therapeutic intervention and improve knowledge of mechanisms of cell death. *CASP8AP2*, an apoptosis facilitator, is highly expressed in patients with low levels of MRD at early time points during therapy and those who have a high EFS and might therefore be used as an additional marker of therapeutic response.[40] On the other hand, higher interleukin-15 gene expression in leukemic cells was associated with central nervous system (CNS) leukemia at diagnosis or CNS relapse[41] and the presence of CC genotype at the interleukin-15 germline SNP with increased expression was associated with MRD positivity.[38]

Role of Hematopoietic Stem Cell Transplantation in Slow Early Responders

The BFM and AIEOP groups together conducted a large randomized study of children with very-high-risk ALL comparing chemotherapy versus transplantation with a matched related donor (if one was available) during first remission.[34] In this series, transplantation improved outcomes in all subgroups of very-high-risk cases, including those with induction failure (5-year DFS, 56% in the transplantation arm vs. 26.5% in the chemotherapy arm) and patients with poor prednisone response associated with a T-cell phenotype and/or hyperleukocytosis (62.4% vs. 54.3%). The Italian PETHEMA-ALL-93 trial included 60 patients with a slow or partial response to induction therapy (≥ 25% blasts at day 14 or 5%–25% blasts at day 35, respectively) randomized to receive chemotherapy, autologous transplantation, or allogeneic transplantation.[6] Five-year DFS did not differ between the 3 groups. The conflicting results between the two studies might be explained in part by the longer time to transplantation and the lack of total body irradiation in the conditioning regimen in the PETHEMA trial. In a small COG series of children with induction failure, 5 of 7 children are alive more than 5 years after transplantation with stem cells from a matched sibling donor.[42]

Alternative donor sources are increasingly used for transplantation in children with leukemia. A higher degree of mismatch is acceptable with cord blood units and outcomes are comparable with those of allele-matched transplants.[43,44] Importantly, cord blood units can be obtained

with a shorter waiting period and from a larger recipient pool, particularly for ethnic minorities that have a lower probability of having a suitably matched unrelated donor. Outcomes of transplantation from nonsibling donors (matched unrelated and mismatched family) are also encouraging.[45] Patients with high-risk T-cell ALL defined by a poor initial response treated on BFM-90 and BFM-95 were eligible for SCT.[45] The 5-year DFS with chemotherapy alone was 42%, and improved to 65% and 69% with transplantation from sibling and nonsibling donors, respectively. As expected, relapse was more common after sibling transplantations and treatment-related mortality more frequent after nonsibling transplantations. The international BFM group and the European Group for Blood and Marrow Transplant have initiated an international prospective study of children who require transplantation for ALL.[46] Defined indications for transplantation in first remission include the presence of t(9;22) or t(4;11) and response-based criteria (poor prednisone response, blasts detected by morphologic examination of bone marrow at the end of remission induction, and positive MRD at week 12 of treatment). Results from this multicenter study will provide data about transplantation indications, donor selection, optimal regimens for graft-versus-host disease prophylaxis, and supportive care. In parallel, as data on the effect of novel and biologically based targeted therapies in combination with conventional chemotherapy mature, indications for transplantation are likely to evolve.

Infant Acute Lymphoblastic Leukemia

Although ALL in infants younger than 1 year comprises only 2%–3% of childhood ALL, this group has an inferior outcome due in part to high-risk presenting features (eg, high leukocyte count, bulky extramedullary disease, CD10 negativity, immature pro-B phenotype), and an increased incidence of treatment-related toxicities.[47] Eighty percent of infants with ALL harbor rearrangements of the *MLL* gene located on chromosome 11q23. *MLL* plays a critical role in hematopoiesis by regulating the *HOX* group of genes, which sequentially influence hematopoietic stem cell renewal and leukemogenesis.[48]

Risk Stratification in Infant Acute Lymphoblastic Leukemia

Data from multiple clinical trials in infant ALL have been useful in investigating prognostic factors unique to this subset of patients.[49,50] Age younger than 6 months, extreme hyperleukocytosis (> 300,000 white blood cells/μL), CD10 negativity, and the presence of *MLL* rearrangement negatively effect outcome. The type of the partner gene fused to *MLL* does not seem to influence outcome. Studies by the BFM group and the international ALL protocol Interfant-99 confirmed the prognostic effect of prednisone response.[17,49] For patients treated on Interfant-99, the 4-year EFS was 56.4% for prednisone-good responders and 29.8% for prednisone-poor responders. Therefore, subsets of infants with the poorest prognostic features can be identified for additional therapeutic interventions.

Treatment of Infant Acute Lymphoblastic Leukemia

Infants treated with conventional ALL protocols fare poorly and relapse early.[51] In vitro studies have demonstrated that infant ALL blasts have a characteristic drug resistance profile: they are relatively more resistant to glucocorticoids and L-asparaginase while sensitive to cytarabine and cladribine than blasts of other patients with precursor B-ALL.[52] Intensive treatment strategies incorporating drugs such as high-dose cytarabine have been implemented globally. Interfant-99 is the largest infant ALL clinical trial to date and included 482 patients from 17 study groups in 22 countries.[49] Patients were risk stratified based on prednisone response. The treatment regimen was a hybrid that contained some elements of therapy used in protocols for acute myeloid leukemia (AML), including high-dose cytarabine in consolidation. There was a modest improvement in survival (4-year EFS of 47%) without increased toxicity for patients in Interfant-99 compared with previous smaller studies by various study groups.[53] An extra

late reintensification course before continuation therapy failed to improve outcome. Because most relapses occurred early, the subsequent Interfant-06 trial is assessing the efficacy of 2 early "AML-like" intensification blocks. Interestingly, a Russian study showed that adding all-*trans*-retinoic acid to conventional intensive chemotherapy is well tolerated by infants with *MLL*-rearranged ALL.[54] Early outcomes for the 15 patients treated with this regimen are promising, with an 18-month EFS of 73%, but it is unclear whether this regimen and others that reduce the rates of early relapse will provide sustained improvement in EFS.

Implications of Biology of Infant Acute Lymphoblastic Leukemia

Novel strategies are needed as further intensification including stem cell transplantation leads to increased toxicities without a proportionate increase in EFS. Gene expression studies have demonstrated that *MLL*-rearranged leukemias are a distinct entity characterized by deregulation of multiple *HOX* genes.[55] FLT3, a receptor tyrosine kinase that plays a role in promoting cell proliferation and transformation is overexpressed in *MLL*-rearranged ALL, a finding that led to the pursuit of FLT3 inhibitors as targeted therapy for this disease.[56,57] Convincing preclinical observations have prompted the COG to initiate a phase III trial wherein infants with *MLL*-rearranged ALL are being randomized to intensive chemotherapy with or without lestaurtinib (CEP-701™), an oral, highly selective small-molecule FLT3 inhibitor.[53,58] The sequence of administering lestaurtinib with chemotherapy is important: chemotherapy followed by lestaurtinib is markedly synergistic in in vitro experiments, whereas there is antagonism if the sequence is reversed.[59] Another potential lead for targeted therapy from gene expression studies is the underexpression of the tumor suppressor *FHIT* in *MLL*-rearranged ALL. *FHIT* is silenced by methylation, and exposure to the demethylating agent decitabine restores *FHIT* activity and leads to apoptosis.[60] Decitabine is currently under investigation in patients with relapsed or refractory leukemias (NCT00042796 at www.ClinicalTrials.gov).

Outcomes for infants with *MLL*-germline ALL are better than those with *MLL*-rearranged ALL (4-year EFS of 74% vs. 37% on Interfant-99),[49] but still not as good as those of older children with ALL. The significant toxicity of intense infant ALL regimens may account for this difference. *MLL*-germline infant ALL is often CD10 positive and clinically behaves more like noninfant childhood ALL; therefore, less intense therapy of longer duration, such as that used for standard precursor B-lineage ALL, may suffice. Current trials, including the St. Jude Total XVI protocol, do not intensify therapy for infants with MLL-germline ALL who have a satisfactory early response to remission induction therapy.

Role of Transplantation in Infant Acute Lymphoblastic Leukemia

The role of transplantation for infants with ALL in first remission remains controversial. Several early studies showed that the transplant was not of benefit; in fact, some showed worse outcomes in infants transplanted in first remission even after adjusting for presenting clinical features and waiting time to transplantation.[47] Although Interfant-99 was not designed to study the role of transplantation, the 4-year DFS for 37 high-risk patients who were transplanted was not significantly different from that of infants who received chemotherapy alone (50% vs. 37%; $P = .19$). On the other hand, in COG trials 1953 and 9407, infants with *MLL*-rearranged ALL were prospectively randomized to transplantation or chemotherapy after completing reinduction I. Conditioning regimens varied by institution, but the hazard ratio for treatment failure for transplantation was 1.45, a result inferior than that of chemotherapy.[61] Reports from some single institutions argued for transplantation.[62,63] Of 14 infants with *MLL*-rearranged ALL who received transplantation at the Fred Hutchinson Cancer Research Center, 1 relapsed and 2 died of pneumonia, and the 3-year EFS was 73%.[62] In the Japanese Infant leukemia studies 96 and 98, transplantation was performed in first remission for 49 of 80 *MLL*-rearranged infants who survived remission induction and had a compatible stem cell source; 8 of them died of transplantation-related causes, and 14 relapsed.[64] Long-term side effects in the 36

survivors were significant and included short stature in 23 patients, chronic graft-versus-host disease in 5, hypothyroidism in 5, skin abnormalities in 12, ophthalmic complications in 5, pulmonary dysfunction in 6, and neurologic complications in 6. It is also suspected that the graft-versus-leukemia effect plays a limited role in infant ALL.[42]

In our opinion, early intensification strategies and carefully planned trials of newer agents, including molecularly defined targeted drugs, might prove more beneficial than transplantation in patients with this highly aggressive leukemia. Although transplantation might benefit selected high-risk patients, the high incidence of transplantation-related mortality and major long-term side effects without a proven increase in EFS do not justify widespread use of this modality for infants with ALL.

Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

Philadelphia chromosome positivity in ALL portends a poor prognosis even in the era of intensive chemotherapeutic regimens. Although more than 95% of patients achieve an adequate response to induction therapy, these remissions are shallow and short-lived.[65] Historically, matched-related transplantation had been recommended for children with this subtype of ALL, especially those with poor early response to induction therapy. The advent of imatinib and other tyrosine kinase inhibitors might revolutionize the treatment of Ph^+ ALL.

Tyrosine Kinase Inhibitors

The arrival of imatinib heralded the era of molecularly targeted medicine to this century.[66] Imatinib inhibits the activity of Abelson kinase by binding to the activation site and trapping it into an inactive form. Responses obtained with imatinib monotherapy were not sustained in ALL as they were in chronic myeloid leukemia (CML), and thus subsequent studies evaluated combinations of imatinib with chemotherapy. Concurrent administration of imatinib with a multiagent regimen in an adult cohort led to molecular remission in 54% of patients compared with 19% in those who received an alternating regimen.[67] In a recent report, 93 children with Ph^+ ALL were given imatinib (340 mg/m^2 per day) in combination with an intensive chemotherapy backbone.[68] For safety reasons, the duration of exposure was increased in a step-wise fashion from 42 days in the first cohort of patients to 280 days in the fifth cohort. Excessive toxicities were not observed and the early result for the 44 patients in the fifth cohort was outstanding with a 3-year EFS of 80% ± 11% (standard error), which was superior to 35% ± 4% in the 120 historical controls. Importantly, the 3-year EFS rate (88% ± 11%) for the 25 patients in the fifth cohort who were treated with chemotherapy plus imatinib was at least comparable to the patients in all cohorts treated with either matched-related transplantation (57% ± 22%, n = 21) or matched-unrelated transplantation (72% ± 19%; n = 11). The 3-year rate (50% ± 35%) for the 9 patients with induction failure was also impressive. In fact, the minimal residual disease level at the end of induction failed to predict treatment outcome in the fifth cohort. Longer follow-up is needed to determine if imatinib improves the cure rate or merely prolongs DFS.

Resistance to imatinib often develops in patients with Ph^+ ALL. A common mechanism of resistance is the development of point mutations within the kinase-binding domain of *BCR-ABL*, most often in the P-loop or at codon 315 (T315I). By using sensitive detection methods such as denaturing high-performance liquid chromatography, these mutations can be detected in a small subclone of leukemic cells in 40% of newly diagnosed patients, but in the dominant clone in 90% at relapse, thus implying selective pressure of the resistant clone after treatment with tyrosine kinase inhibitors.[69] Additional mechanisms leading to imatinib resistance include gene amplification of *BCR-ABL*, overexpression of the protein, and activation of the SRC family kinases. The SRC family kinases play a role in leukemic transformation by BCR-ABL in Ph^+ ALL but not CML.[70] Pathways downstream of BCR-ABL including Ras and

phosphatidylinositol 3-kinase (PI3K) are also essential in maintaining the leukemic process. Circumventing resistance mechanisms by newer-generation tyrosine kinase inhibitors and drugs targeting multiple pathways are some approaches being pursued.

Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors effective in patients resistant to imatinib, except those with the T315I mutation. Dasatinib is a multikinase inhibitor targeting several tyrosine kinases, including BCR-ABL and SRC kinases. It is 325 times more potent than imatinib, binds to the active and inactive forms of BCR-ABL, and has excellent CNS penetration.[71,72] A review of 4 single-arm trials in adult patients with imatinib-resistant or imatinib-intolerant Ph+ malignancies (CML and ALL) reported durable responses in patients and led to FDA approval in June 2006.[73] Common adverse events included myelosuppression, gastrointestinal symptoms, and fluid retention. Because dasatinib is a substrate of CYP3A4, concomitant use of inducers or inhibitors of this enzyme (eg, barbiturates, azoles) should be avoided. Acid-blocking agents should also be avoided, because an elevated gastric pH can reduce absorption of dasatinib.[73] Preliminary results of a pediatric phase I study have recently been reported,[74] but ongoing clinical trials by various groups, including St. Jude, are testing this promising agent in children with newly diagnosed Ph^+ ALL. Nilotinib is a derivative of imatinib in which modification of the aminopyrimidine backbone resulted in improved binding and a 30-fold increase in potency.[75] Third-generation tyrosine kinase inhibitors are being actively developed, especially to address the problematic T315I mutation that confers resistance to all existing BCR-ABL–specific tyrosine kinase inhibitors. Dual aurora/ABL kinase inhibitors (eg, MK-0457), heat-shock protein inhibitors (eg, geldanamycin analogues), and FLT3 inhibitors (eg, KW2449) show activity against leukemic cells with the T315I mutation and clinical trials of these agents are ongoing.[76]

Role of Transplantation in Philadelphia Chromosome–Positive Acute Lymphoblastic Leukemia

Philadelphia chromosome–positive ALL, similar to other subtypes of ALL, is a heterogeneous disease. In Ph^+ ALL, good prognostic features include age younger than 10 years, presenting WBC count < 50,000/μL, and a good response to remission induction chemotherapy.[77] Further prognostication might be possible by quantifying MRD by PCR for the *BCR-ABL* fusion transcript.[78] A benefit of transplantation in first remission has been observed in several trials in adults and children that compared transplantation and chemotherapy, in which patients were "biologically randomized" by the availability of a suitable donor.[77,79] In 267 children with Ph^+ ALL diagnosed between 1986 and 1996, 5-year DFS was 25% with chemotherapy alone compared with 72% for patients receiving transplantation from a matched related donor.[77] Evidence suggests that graft-versus-leukemia effect in Ph^+ ALL is strong because grade II or higher acute graft-versus-host disease was associated with a lower risk of relapse and donor lymphocyte infusions were able to salvage some patients who relapsed after transplantation.[80] As tyrosine kinase inhibitors are incorporated into therapy, the role of transplantation for Ph^+ ALL continues to evolve. In a recent Japanese phase II clinical trial that used combination chemotherapy incorporating imatinib in adults with Ph^+ ALL, the 1-year overall survival for patients who went on to receive transplantation was 73.3%, which was comparable to patients who were not candidates for transplantation and received chemotherapy alone (84.8%).[81] However, unlike other subgroups of ALL, relapse rates are still high at years 3 and 4 after diagnosis.[77] Because children fare significantly better than adults with the same subtypes of leukemia, it is possible that the excellent treatment result as mentioned earlier for children with Ph^+ ALL who were treated with imatinib and intensive chemotherapy will persist with longer follow-up. If so, the indications for transplantation in children with Ph^+ disease will be changed substantially.

Additional Subgroups of High-Risk Acute Lymphoblastic Leukemia

Though severe hypodiploidy (modal chromosome number less than 44 in the leukemic clone) is rare and comprises only 1% of cases of childhood ALL, outcome is much inferior to nonhypodiploid ALL. Pooled data from 130 non-Ph^+ hypodiploid patients collected by 10 international study groups revealed 8-year EFS of 38%.[2] Thus, patients with hypodiploid ALL are currently treated on higher-risk protocols. The COG has reported a 2-year EFS of 57% for 28 patients treated with intensified chemotherapy and 67% for 13 children who received a stem cell transplantation. These results are superior to the EFS of 44% in historic controls.[33]

Intrachromosomal amplification of chromosome 21 is a recently recognized recurrent abnormality associated with inferior prognosis in ALL.[82] Patients with this cytogenetic abnormality enrolled on the current UK MRC trial (NCT00222612) are treated on the high-risk arm. More recently, within the past year, modern genome-wide studies of leukemic blasts have detected genetic lesions such as deletions or mutations in the *IKZF1* gene[83] or activating mutations in JAK tyrosine kinases[84] as indicators of inferior outcome in patients with high-risk ALL. These and subsequent validation and functional studies will provide insights into the pathogenesis of leukemogenesis in various genetically defined subgroups of ALL and possibly point to targets for therapeutic intervention. An important high-risk T-cell ALL subtype has been described by Coustan-Smith et al.[85] Using complementary immunophenotyping and high-throughput genomic tools, they have identified approximately 12% of patients with T-cell ALL to have characteristic stem cell–like features in the leukemic blasts. Patients with this early T-cell precursor leukemia have an extremely high probability of treatment failure: 72% at 10 years versus 10% for patients with typical T-cell ALL. In an attempt to improve outcome for patients with the early T-cell precursor phenotype, they are offered a stem cell transplantation in first remission in the ongoing St. Jude study.

Conclusion

Tailoring therapy to the predicted risk of relapse is vital to improve cure rates and minimize toxicities in childhood ALL. In addition to biologic and clinical features of the tumor and the host, close monitoring of residual disease at various time points has proven essential in determining prognosis (Table 2). Recent genome-wide studies aim to identify gene expression signatures at diagnosis that are predictive of early response and long-term outcome.[38,40,86] It remains to be seen whether these signatures will be incorporated into risk stratification algorithms in future prospective clinical trials.

Certain high-risk features have been abrogated by current intensive regimens or specific interventions. For example, patients with the *E2A/PBX* fusion were once considered a high-risk group, but are now treated on the same risk-directed regimens as other patients with precursor B-ALL.[87] Patients with hyperleukocytosis and T-cell ALL are at a high CNS relapse; this risk is minimized by additional CNS prophylaxis in the form of cranial irradiation (12 Gy) or with intensive intrathecal therapy.[88] Importantly, many relapses still occur in patients initially classified as standard risk and efforts are under way to identify additional subgroups among them who are at increased risk of relapse.

Rapid progress in the development of new chemotherapy agents, targeted therapies, safer and more available stem cell transplantation, improved supportive care, and successful intensification of therapy for high-risk and very-high-risk patients with ALL have improved outcomes in the past decade and promise to cure even more children in the coming decade.[89,90] With increased understanding of the mechanisms of leukemic cell transformation and the development of drug resistance, as well as the genetic influences on a patient's response to

chemotherapy,[91,92] we are close to an era of personalized therapy for ALL, in which therapy will be based on the unique molecular targets and pharmacodynamics of individual patients.

Acknowledgments

Supported in part by CA21765 from the National Cancer Institute and by the American Lebanese Syrian Associated Charities (ALSAC).

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Table 1

Summary of Criteria and EFS Rates for Higher-Risk (High-Risk and Very-High-Risk) Childhood ALL From Various Clinical Trials

Study	Year	Number and Proportion of Patients in High-Risk and/or Very-High-Risk Categories	Criteria: High-Risk and/or Very-High-Risk	Event-Free Survival
COG AALL03B1 Classification study **Carroll et al**[3]	Ongoing	HR, 1841 (33%) VHR, 390 (7%) (as of 12/07/07; B-precursor ALL only)	HR: age ≥ 10 years; WBC ≥ 50,000/μL; no adverse cytogenetic features VHR: induction failure; t(9;22); extreme hypodiploidy (< 44 chromosomes) *MLL* rearrangement without M1 marrow by day 15 and/or MRD ≥ 0.1% at end of induction	Too early to determine
SJCRH Total XIIIB **Pui et al**[7]	1994–1998	130 (53%)	Age ≥ 10 years; WBC ≥ 50,000/μL; extramedullary disease; T-cell ALL; t(9;22) t(1;19); *MLL* rearrangement; near-haploidy; ≥ 5% marrow blasts at day 19	73% ± 5.5% (5-year)
DFCI 95-01 **Moghrabi et al**[8]	1996–2000	219 (45%)	Age ≥ 10 years or < 1 year; WBC ≥ 50,000/μL; any blasts in CSF at diagnosis mediastinal mass; T-cell ALL; t(9;22)	76% ± 3% (5-year)
BFM ALL-95 **Moricke et al**[4]	1995–2000	254 (12%)	Poor prednisone response; ≥ 5% blasts on day 33; t(9;22); t(4;11)	49.2% ± 3.2% (6-year)
AIEOP ALL-95 **Aricò et al**[5]	1995–2000	244 (14%)	Poor prednisone response; t(9;22); age < 1 year with $CD10^{-}$ ALL or t(4;11) ≥ 5% marrow blasts on day 43	51% ± 3.2% (10-year)
PETHEMA ALL-93 **Ribera et al**[6]	1993–2002	106[a]	Age < 1 year; WBC ≥ 300,000/μL in B-lineage, ≥ 100,000/μL in T-cell ALL; t(9;22) *MLL* rearrangement; > 25% marrow blasts at day 14; 5%–25% marrow blasts at day 35	45% ± 8% (5-year DFS)
CCLG-EORTC 58881 **Vilmer et al**[9]	1989–1998	327 (16%)	Poor response to prednisone; no CR at end of induction; t(9;22); t(4;11)	48% ± 2.9% (5-year)
NOPHO ALL-92[b] **Saarinen-Pihkala et al**[10]	1992–2000	426 (29%)	HR: WBC ≥ 50,000/μL; extramedullary involvement; T-cell ALL lymphomatous features; t(9;22); t(4;11); > 25% marrow blasts on day 15 ≥ 5% marrow blasts on day 29; VHR: age ≥ 5 years at diagnosis and one of the following: CNS disease; lymphomatous features; T-cell ALL with WBC ≥ 50,000/μL > 25% marrow blasts on day 15; ≥ 5% marrow blasts on day 29	61% ± 3% (9-year)

Study	Year	Number and Proportion of Patients in High-Risk and/or Very-High-Risk Categories	Criteria: High-Risk and/or Very-High-Risk	Event-Free Survival
TCCSG LL99-15[b] **Manabe et al**[11]	1999–2003	179 (24%)	WBC ≥ 100,000/μL and day 8 peripheral blasts ≥ 1/μL WBC ≥ 20,000/μL and day 8 peripheral blasts ≥ 1000/μL Age ≥ 7 years and day 8 peripheral blasts ≥ 1000/μL WBC 50–100,000/μL and age > 10 years and day 8 peripheral blasts ≥ 1/μL T-cell ALL with day 8 peripheral blasts ≥ 1/μL t(9;22); *MLL* rearrangement	57.8% ± 4.1% (4-year)
CCG 1961[b] **Seibel et al**[12]	1996–2002	2078[a]	Age ≥ 10 years; WBC ≥ 50,000/μL	71.3% ± 1.6% (5-year)
COALL 92[b] **Harms et al**[13]	1992–1997	274 (53%)	Age ≥ 10 years; initial WBC count ≥ 25,000/μL; Pro-B ALL; T-cell ALL t(9;22); no CR by day 29	73% ± 5% (randomized to6-thioguanine)80% ± 4% (randomized to6-mercaptopurine) (median observation time 7.6 years)

[a] Only higher-risk patients eligible.

[b] Infants excluded.

Abbreviations: ALL = acute lymphoblastic leukemia; CNS = central nervous system; CR = complete remission; DFS = disease-free survival; EFS = event-free survival; HR = high-risk; MLL = mixed-lineage leukemia; MRD = minimal residual disease; VHR = very high-risk; WBC = white blood cells

Table 2

Feature of the Host and the Tumor That Play a Role in Response to Therapy and Current Treatment Strategies for Select Subgroups of High-Risk ALL

Disease Feature	Slow Early Responders	MLL-Rearranged Infant ALL	Ph-Positive ALL
Host	- Pharmacogenetics - Bone marrow microenvironment	- Pharmacokinetics - Inability to tolerate toxic regimens	- Older age
Leukemia	- Tumor genetics	- High tumor burden - Intrinsic drug resistance - Primitive cell origin, myeloid features	- Multiple activated oncogenic pathways - Resistance to standard chemotherapy
Treatment	- Augmented therapy - Novel agents - Transplantation	- Novel agents - FLT2 inhibitors - Hybrid regimens	- Tyrosine kinase inhibitors - Transplantation

Abbreviations: ALL = acute lymphoblastic leukemia; Ph = Philadelphia chromosome