Review Article

Adult Acute Lymphoblastic Leukemia

Concepts and Strategies

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Acute lymphoblastic leukemia (ALL), a clonal expansion of hematopoietic blasts, is a highly heterogeneous disease comprising many entities for which distinct treatment strategies are pursued. Although ALL is a success story in pediatric oncology, results in adults lag behind those in children. An expansion of new drugs, more reliable immunologic and molecular techniques for the assessment of minimal residual disease, and efforts at more precise risk stratification are generating new aspects of adult ALL therapy. For this review, the authors summarized pertinent and recent literature on ALL biology and therapy, and they discuss current strategies and potential implications of novel approaches to the management of adult ALL. ***Cancer* 2010;116:1165–76.** © *2010 American Cancer Society.*

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Acute lymphoblastic leukemia (ALL) remains 1 of the most challenging adult malignancies, especially with respect to therapy. Immunophenotyping, cytogenetic-molecular studies, and, more recently, high-resolution genome-wide screening are characterizing ALL as a heterogeneous disease with distinct manifestations and prognostic and therapeutic implications.[1] Copying ALL treatment algorithms that have led to cures for most children with ALL also has resulted in significant improvements in adult ALL therapy, although long-term disease-free survival rates of 40% remain inferior. Given this background, currently, it is commonly accepted that a "1-glove-fits-all" approach has become obsolete. Instead, the ongoing molecular dissection of subtypes, the refinement of mulitagent chemotherapy and development of new and targeted drugs, the elaboration of risk-adapated therapies and reassessment of transplantation indications, comprehension of the kinetics of residual disease, and an increasing grasp of the impact of pharmacogenomics and drug resistance are the mainstays of up-to-date management, and are expected to contribute to improvements in the prognosis of adult ALL.

Epidemiology, Etiology, Clinical Presentation, and Diagnosis

The age-adjusted overall incidence of ALL in the United States is 1.5 per 100,000 population with peaks between ages 2 years and 5 years and again after age 50 years.[2] ALL is more frequent among Caucasians, in affluent societies, and in urban areas, giving rise to speculation about socioeconomic factors in its etiology.[3-5] Investigations also have focused on genetic variability in drug metabolism, DNA repair, and cell-cycle checkpoints that may interact with the environmental, dietary, maternal, and other external factors to affect leukemogenesis.[1,6,7] Most reports about etiologic associations remain isolated and conflicting.

Clinical manifestations at presentation include constitutional symptoms (fevers, night sweats, weight loss), easy bruising or bleeding, dyspnea, dizziness, and infections. Extremity and joint pain may be the only presenting symptoms. Less than 10% of patients have symptomatic central nervous system (CNS) involvement, although the frequency is higher in patients with mature B-cell ALL. Chin numbness may be a subtle indicator of cranial nerve involvement. T-lineage ALL with a mediastinal mass can cause stridor and wheezing, pericardial effusions, and superior vena cava syndrome.

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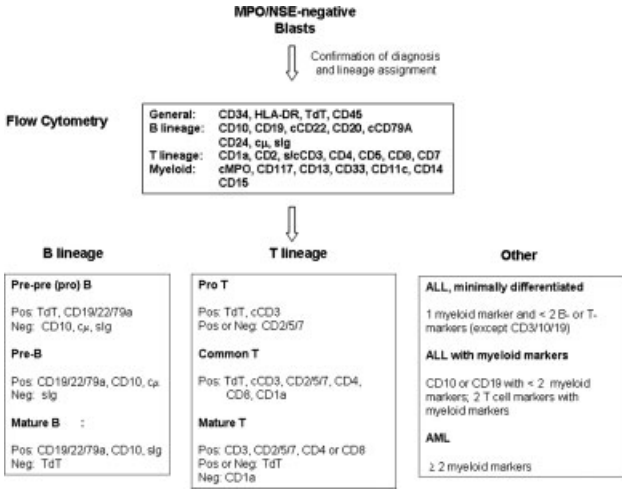

Figure 1. Flow cytometric diagnosis of acute lymphoblastic leukemia (ALL) is illustrated. MPO indicates myeloperoxidase; NSE, nonspecific esterase; c, cytoplasmic; s, surface Pos, positive; Neg, negative; AML, acute myeloid leukemia.

Testicular involvement is rare in adults. Except for mature B-cell ALL, involvement of the gastrointestinal tract also is infrequent.

Because leukemic lymphoblasts lack specific morphologic and cytochemical features, the assessment of immunophenotype by flow cytometry (Fig. 1) and the identification of distinct cytogenetic-molecular abnormalities have become essential and are part of the World Health Organization Classification of Neoplastic Diseases of Hematopoietic and Lymphoid Tissues.[8] The ambiguous expression of myeloid markers (CD13, CD33, CD14, CD15, CDw65) with lymphoid markers is common, especially in ALL with translocations t(9;22), t(4;11), and t(12;21). Although the presence of myeloid-associated antigens lacks prognostic significance,[1,9,10] it can be useful in distinguishing leukemic cells from normal hematogones and in monitoring patients for minimal residual disease (MRD).[11]

Table 1. Cytogenetic and Molecular Abnormalities in Acute Lymphoblastic Leukemia

		Frequency, %	
Karyotype	Gene(s)	Adult	Children
T(9;22)(q34;q11)	*BCR-ABL1*	15-25	2-3
Del(11)(q22)	*ATM*	25-30[a]	15[a]
T(14q11-q13)	*TCR*α and *TCR*δ	20-25[c]	10-20[b]
Del(9)(p21-22)	*CDKN2A* and *CDKN2B*	6-30	20
T(1;14)(p32;q11)	*TAL-1*	10-15	5-10
Hyperdiploidy	—	2-15	20-26
+8	—	10-12	2
Del(7p)	?	5-10	<5
T(10;14)(q24;q11)	*HOX11*	5-10	<5
Hypodiploidy	—	5-10	5-7
Del(11)(q23)	*MLL*	5-10	<5
Del(6q), t(6;12)	?	5	<5
T(8;14), t(8;22), t(2;8)	*c-MYC*	5	2-5
T(14q32)	*IGH, BCL11B*	5	?
Extrachromosome 9q	*NUP214/ABL*		?
Del(13)(q14)	*miR15/miR16*	<5	<5
T(1;19), t(17;19)	*TCF3-PBX1, E2A-HLF*	<5	3-5[c]
Del(5)(q35)	*HOX11L2*	<2	<2
T(5;14)(q35;q32)	*HOX11L2*	1	2-3
Del(9)(q32)	*TAL-2*	<1	<1
Del(12p) or t(12p)	*ETV6-RUNX1*	<1[b]	20-25[d]

T indicates translocation; *BCR-ABL1*, bcr/c-abl oncogene 1, receptor tyrosine kinase gene fusion; Del, deletion; *ATM*, ataxia telangiectasia mutated; *TCR*α and *TCR*δ, T-cell receptor alpha and delta, respectively;*CDKN2A* and *CDKN2B*, cyclin-dependent kinase inhibitor 2A and 2B, respectively; *HOX11*, T-cell leukemia homeobox 1; *MLL*, myeloid/lymphoid or mixed-lineage leukemia; t, translocation; *c-MYC*, v-myc myelocytomatosis viral oncogene homolog (avian); *IGH*, immunoglobulin heavy locus; *BCL11B*, B-cell chronic lymphocytic leukemia/lymphoma; *NUP214*, nucleoporin 214 kDa; *ABL*, c-abl oncogene, receptor tyrosine kinase; *miR15/miR16*, microRNA 15/microRNA 16; *TCF3-PBX1*, transcription factor 3/pre-B-cell leukemia homeobox 1 fusion transcript; *E2A-HLF*, DNA binding protein-hepatic leukemia factor acute lymphoblastic leukemia chimera; *HOX11L2*, orphan homeobox gene; *TAL-2*, T-cell acute lymphocytic leukemia 2; *ETV6-RUNX1*, ets variant 6/runt-related transcription factor 1 gene fusion.

[a]Determined by loss of heterozygosity.

[b]In patients with T-cell acute lymphoblastic leukemia, the overall incidence was <10%.

[c]Differed substantially by race (2%-3% in white patients and approximately 12% in black patients).

[d]Determined by polymerase chain reaction or fluorescent in situ hybridization analysis.

Cytogenetic-Molecular Abnormalities in Acute Lymphoblastic Leukemia

The identification of cytogenetic and molecular abnormalities provides prognostic information, markers for therapy (eg, *BCR-ABL1*) and targets for drug development, and pathobiologic insights (Table 1).[12-15] In many situations (eg, numerical abnormalities), this information is far more predictive for children than for adults and often has weaker associations with prognosis in the latter group.[16] Therefore, the difficulty in extrapolating pediatric data to adult ALL should be kept in mind. The most frequent (15% to 30%) and clinically relevant structural abnormality in adult ALL remains translocation t(9;22)(q34;q11) (Philadelphia chromosome [Ph]) with the *BCR-ABL1* fusion.[17] Patients with Ph-positive ALL are older, present with higher white blood cell and blast counts, and often share myeloid markers.[18] Patients with Ph-positive ALL used to have a dismal prognosis with little chance of a cure other than stem cell transplantation (SCT). Recent combinations of tyrosine kinase inhibitors

(TKIs) with chemotherapy have produced promising results, although the impact on long-term disease-free survival remains unclear.

Several molecular markers are identified as key players in leukemogenesis. Activating mutations of *NOTCH-1*, a transmembrane receptor-encoding gene that regulates normal T-cell development, have been detected in the majority of human T-cell ALLs.[19] In *NOTCH-1*–dependent T-cell lymphomas, the activity of cell cycle-regulatory proteins is increased, leading to accelerated cell proliferation and expression of the leukemic phenotype. Unraveling of the pathways of aberrant *NOTCH-1* activation has led to clinical trials of targeted agents (like γ-secretase inhibitors) and combinatorial approaches (eg, with inhibitors of NOTCH and cell-cycle proteins).[20] SMAD family member 3 (Smad3) is part of the chain of transforming growth factor (TGF)-β–dependent signaling pathways, and its loss was identified in samples from children with T-lineage ALL. That loss, together with loss of the cyclin-dependent kinase inhibitor B1 (p27Kip1), reportedly acted synergistically in T-cell leukemogenesis in mice.[21] Epigenetic changes, including hypermethylation of tumor-suppressor genes or microRNA genes and hypomethylation of oncogenes, are common and have been identified in up to 80% of patients.[22-24] Interactions between methylation changes and organization of histone complexes have become a larger focus of research, not least because many available drugs (eg, DNA methyltransferase inhibitors, histone deacetylase inhibitors) are able to target various steps involved in epigenetic alterations.[25]

Microarray assays provide gene expression profiles, which may help to more accurately distinguish subtypes, stratify patients according to risk and response, identify genetic markers associated with drug sensitivity and resistance pathways, and yield useful insights into the pathogenesis and biology of ALL.[15,26-30] For example, a genome-wide study recently identified a subgroup of very high-risk B-lineage ALLs with a genetic profile similar to that of ALL with *BCR-ABL1* fusion, characterized by Ikaros family zinc finger 1 (IKZF1) deletion.[30] However intriguing the possibilities, issues related to reproducibility, statistical significance, and practical applications still are not resolved sufficiently for gene expression profiling to be ready for clinical use. The emergence of proteomics also raises questions about the significance of gene expression versus protein expression.

Pharmacogenetics and pharmacogenomics may determine how ALL blasts respond to drugs and highlight mechanisms of drug resistance.[15,31,32] Hyperdiploid cells accumulate more methotrexate polyglutamates as they possess extra copies of the gene encoding reduced folate carrier, an active transporter of methotrexate.[33] Blasts with an ets variant 6/runt-related transcription factor 1 (*ETV6-RUNX1*) fusion are more sensitive to purine analogs and asparaginase.[34] Cells that harbor myeloid/lymphoid or mixed-lineage leukemia (*MLL*) rearrangements are more sensitive to cytarabine, possibly because of the overexpression of cellular cytarabine transporters.[35]

Associations also have been identified between germline genetic characteristics (genes that encode drug-metabolizing enzymes, transporters, and drug targets) and drug metabolism and sensitivity to chemotherapy. Rocha et al[36] studied 16 genetic polymorphisms that affected the pharmacodynamics of antileukemic agents and observed that, among 130 children with high-risk disease, the glutathione *S*-transferase μ 1 (*GSTM1*) non-null genotype was associated with a higher risk of recurrence, which was increased further by the thymidylate synthetase (*TYMS*) 3/3 genotype. Other polymorphisms of relevance involve the methylenetetrahydrofolate reductase gene (*MTHFR*) and the thiopurine methyltransferase gene (*TPMT*).[37] In some patients, increased sensitivity to therapeutics is associated with more side effects (including second cancers) as much as greater sensitivity and improved outcome. It is noteworthy that the pharmacogenetics of bone marrow mesenchymal cells also can affect treatment outcomes: High levels of asparagine synthetase in mesenchymal cells can protect ALL cells from asparaginase treatment.[38] Recent genome-wide pharmacogenomic studies are directed not only to the optimal use of existing drugs for individual patients but also to the discovery of new drugs.[1]

Prognostic Models in Acute Lymphoblastic Lymphoma

Prognostic models for ALL have been refined continuously since the first attempts at prognostication back in the 1980s.[15,39] Over the years, improvements in therapy have rendered invalid the prognostic significance of some variables that once were considered important (eg, the prognosis of T-cell ALL or mature B-cell ALL). Table 2 summarizes prognostic variables that have been established by several groups in the United States and Europe.[39-43] New information about associations with molecular markers continues to add to an increasingly comprehensive risk stratification of patients. For example, gene expression analysis in T-lineage ALL has demonstrated high expression of the v-ets erythroblastosis virus

Table 2. Unfavorable Prognostic Features

Characteristic	Kantarjian 2004[40]	Hoelzer 1988[39]	Rowe 2005[41] and Lazarus 2006[42]	Le 2006[43]
Age, y	>60	>35	>35	Higher vs lower
WBC, $\times 10^9$/L	>5	>30[a]	>30[a]	Higher vs lower
LDH	NA	NA	NA	Higher vs lower
Time to CR	>1 Course	>4 Wk	—	—
Immunophenotype	B	Pro-B, early and mature T	T lineage	—
Karyotype	t(9;22)		t(9;22)	t(9;22); Misc vs normal
Molecular	*BCR-ABL*	*BCR-ABL; ALL1-AF4*	NA	NA
CNS involvement	Yes	NA	Yes	NA
Minimal residual disease	NA	Persistent	NA	NA

WBC indicates white blood cell count; LDH, lactate dehydrogenase; NA, not available; CR, complete response; Misc, miscellaneous; *BCR-ABL1*, bcr apoptosis facilitator/c-abl oncogene 1 receptor tyrosine kinase gene fusion; *ALL1-AF4*, acute lymphocytic leukemia susceptibility 1/acute mixed-lineage leukemia gene fusion; CNS, central nervous system.
[a]The total was >100 in T-lineage acute lymphoblastic leukemia.

E26 oncogene-like (*ERG*) and the T-cell leukemia orphan homeobox gene (*HOX11L2*) as unfavorable features.[44,45]

Monitoring of MRD after induction and during consolidation has become another powerful predictor of disease recurrence and is used in current trials to stratify standard-risk patients further.[46] Although adults have higher MRD levels at the completion of induction, and the risk of recurrence is higher with low levels of MRD compared with children, continuous MRD assessment at several time points also was predictive in adults.[46,47]

The German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia (GMALL) prospectively monitored 196 patients with standard-risk ALL at up to 9 time points during the first year of therapy with quantitative polymerase chain reaction (PCR) analysis.[46] According to the speed of MRD eradication or the persistence of MRD over time, 3 risk groups were defined with a 3-year risk of recurrence that ranged from 0% (low-risk group) to 94% (high-risk group). A recent update in a larger series of patients predicted that overall survival would range from 80% in the absence of MRD down to 20% in the presence of MRD. MRD monitoring also is important in the setting of hematopoietic SCT (HSCT), with high level of disease before transplantation or persistent residual disease after transplantation conferring a poorer outcome.[47]

Therapy of Frontline Acute Lymphoblastic Leukemia

Starting in the 1960s, researchers at St. Jude Children's Research Hospital designed combination therapies of all available antileukemia drugs that were delivered in a sequence of extended courses of therapy. Similar algorithms were introduced for adult ALL following the basic principles of induction therapy, early intensification and consolidation, CNS prophylaxis, and a prolonged maintenance phase.[48] Subtype-specific, risk-adapted and targeted therapy designs have become major objectives of more recent clinical trials.[49-52] Table 3 summarizes established multiple-drug ALL regimens.

Vincristine, corticosteroids, anthracyclines, and asparaginase remain the backbone of induction therapy.[15] Whereas the type of anthracycline does not play a role, whether higher doses of anthracyclines improve outcome remains disputed.[50,53] Cytarabine, methotrexate, cyclophosphamide, and (less frequently) etoposide, tenoposide, or m-amsacrine are used mainly during early intensification. With complete remission rates approaching 90%, intensification of induction and early consolidation have their greatest impact on remission duration and survival.[50,54] L-asparaginase is a difficult drug for adults and, thus, is underused, although randomized pediatric ALL trials produced better survival when L-asparaginase was given throughout the induction and/or postremission phase.[55] Conversely, the absence of L-asparaginase throughout induction and intensified consolidation during hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (hyper-CVAD) did not appear to affect remission and disease-free survival rates negatively in adults compared with other regimens.[40] Pegasparaginase is a modified form of *Escherichia coli* asparaginase with a longer serum half-life and a reduced risk of hypersensitivity.[56] In Cancer and Leukemia Group B (CALGB) study 9511, pegasparaginase 2000 U/m^2 was given to adult patients with untreated ALL during each of the first 3 courses.[57] Asparagine depletion occurred in 80% of patients and was correlated positively with disease-free and overall survival. Antibodies to pegasparaginase developed in only 3 patients, and the incidence of

Table 3. Acute Lymphoblastic Leukemia Induction Regimens

Regimen	Induction	Consolidation	Maintenance	CR Rate, %	5-Year DFS Rate, %
LALA-94; Thomas & Fiere 2008[51]	P, V, C, D, or Ida	Ara-C, MTZ, or C, Ara-C, 6-MP based on risk	HSCT or MTX/6-MP or additional chemotherapy based on risk	84	30
Hyper-CVAD; Kantarjian 2004[40]	Hyper C, V, A, and D alternating with MD MTX and Ara-C × 8 cycles	See induction	Allo HSCT or 6-MP, V, MTX, P	92	38
UCSF 8707; Linker 2002[52]	P, V, D, and L-Asp	V, P, D, A, Ara-C, VM-26, MTX	6-MP, MTX	93	52
GMALL 05/93; Gokbuget & Hoelzer 2009[49]	Induction 1: P, V, D, MTX, L-Asp; Induction 2: C, Ara-C, 6-MP	HD Ara-C, MTZ, HD MTX, L-Asp, 6-MP	6-MP, MTX	83	35-40
CALGB 8811; Larson 1995[48]	P, V, C, D, L-Asp	C, subq Ara-C, 6-MP, V, L-Asp	6-MP, MTX	85	39 (Ages 30-59 y); 69% (aged <30 y)[a]

CR indicates complete remission; DFS, disease-free survival; LALA, adult acute lymphoblastic leukemia; P, prednisone; V, vincristine; C, cyclophosphamide; D, daunorubicin; Ida, idarubicin; Ara-C, cytarabine; MTZ, mitoxantrone; 6-MP, 6-mercaptopurine; HSCT, hematopoietic stem cell transplantation; Hyper-CVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; MD, moderate dose; Allo, allogeneic; UCSF, University of California-San Francisco; L-Asp, asparaginase; VM-26, teniposide; GMALL, German Multicenter Study Group for Adult Acute Lymphoblastic Leukemia; HD, high-dose; CALGB, Cancer and Leukemia Group B; subq, subcutaneous.
[a]Overall survival at 3 years.

hypersensitivity reactions or pancreatitis was low.[58] There has been interest in the anti-CD20 chimeric monoclonal antibody rituximab based on a reported association between CD20 expression and a higher recurrence rate in patients with pre-B and mature ALL.[59-61]

Postremission therapy includes intensified consolidation and maintenance therapy or HSCT. Because this is a complex sequence of therapies, the optimal type and duration of postremission therapy, the value of further intensifications, and the optimal selection and timing of HSCT still are debated. Although there is a tendency in favor of intensification,[48,62] other trials have raised doubts about the feasibility of prolonged intensified consolidation in adults because of higher rates of toxicities and worse compliance.[63] Therefore, identifying reliable tools for proper patient selection is becoming crucial, and measuring MRD is developing into 1 of these tools.[49,64] Shortened, intensified induction, intensified consolidation, risk-adapted, and extended SCT indications based on MRD have become the basis for recent trials of the GMALL.[49,65] In a study from Italy, MRD testing during Weeks 16 through 22 of therapy was the most significant factor for disease recurrence. Patients who had low or absent MRD levels had significantly better 5-year disease-free and overall survival compared with patients who had MRD.[64]

Maintenance therapy is modified according to ALL subtype: no maintenance for mature B-cell ALL, because most recurrences occur within 12 months, and TKIs for Ph-positive ALL. Nelarabine (see below) in the maintenance of T-lineage ALL is being investigated in clinical trials.

Elderly patients, commonly defined as ages 60 years to ≥65 years, have a worse prognosis than younger patients when they are subjected to the same intense therapies as younger patients. Although remission rates vary widely, their long-term survival probability is <20%.[66] Whereas intensifying chemotherapy in older patients reduces the incidence of leukemia resistance, it also increases the incidence of death in complete remission from myelosuppression-related complications. A lead for the future is indicated by regimens of moderate dose intensity consolidation, like those of the European Working Group for Adult ALL, which reported an 85% remission rate with a 61% 1-year survival probability and a low rate of treatment-related deaths (<10%).[67]

Hematopoietic Stem Cell Transplantation

Appropriate selection of patients and, thus, the timing of HSCT in ALL remains a hotly debated issue.[68-71] Although allogeneic SCT in high-risk patients in first complete remission has been widely accepted, recent data suggest that the benefit of HSCT may extend to standard-risk patients, whereas it may have been overestimated in the high-risk group.

These data primarily derive from the large Medical Research Council (MRC) UKALL XII/Eastern Cooperative Oncology Group (ECOG) E2993 trial, which included 1929 patients ages 15 years to and 59 years.[71] After induction chemotherapy and high-dose methotrexate intensification, all patients who had a human leukemic antigen-matched sibling donor and were aged $\leq$55 years (<50 years before 2004) were assigned to allogeneic HSCT, whereas all others were randomized to chemotherapy versus autologous HSCT. High-risk patients were defined by age >35 years, leukocytosis ($\geq 30 \times 10^9$/L for B-lineage ALL and 100×10^9/L for T-lineage ALL), and Ph-positive ALL. The results can be summarized as follows: 1) The complete remission rate was 90%, and the 5-year survival rate was 43% for all patients; 2) the 5-year survival rate was 53% for Ph-negative patients who had a donor compared with 45% for those who had no donor ($P = .02$); 3) the 5-year survival rate for standard-risk patients was superior for patients who had a donor compared with those who had no donor (62% vs 52%; $P = .02$); 4) the 5-year survival rate for high-risk patients was not significantly different whether patients had a donor or not (41% vs 35%; $P = .2$; transplantation-related toxicity abrogated the effect of a reduction in the recurrence rate); and 5) postremission chemotherapy produced superior event-free and overall survival compared with autologous HSCT ($P = .02$ and $P = .03$, respectively). The most important conclusion from the MRC/ECOG study is that standard-risk patients in first complete remission benefit more from allogeneic SCT than from chemotherapy. These conclusions are not uniformly consistent with results from previous studies, in which, except for high-risk patients, allogeneic SCT has not favored standard-risk patients.[67,72,73] This may be explained in part by differences in the definition of high risk versus standard risk, although most would agree that at least Ph-positive ALL and older age (>35 years, >40 years, or as a continuous variable) constitute criteria for high risk. Furthermore, approximately 60% of adults aged <30 years with standard-risk ALL can be cured with chemotherapy, sparing them from the long-term adverse events associated with allogeneic SCT. It recently was demonstrated that the outcome of adolescents and young adults (AYAs) who were treated on pediatric regimens was superior to the outcome for same group treated on adult regimens (see below), diminishing significantly the need to refer this patient group for transplantation. Further dissection of the standard-risk group (eg, based on levels of MRD) may provide better guidance regarding who should undergo transplantation in first complete remission and who should not. Nevertheless, given the traditionally contentious issue of transplantation versus chemotherapy, opinions will continue to be divided, and it is unrealistic to expect that every single standard-risk patient will be referred for transplantation, which also is not current practice in most major ALL study groups in the United States and Europe.[74,75]

Because up to 70% of patients do not have a matched sibling donor, much work has been invested in improving transplantations from alternative donor sources (partially matched, related donors; matched, unrelated donors; umbilical cord blood). Bishop et al[76] determined outcomes between autologous and matched, unrelated HSCT in 260 adult patients in first or second complete remission. Although treatment-related mortality was higher for patients who underwent HSCT with a matched, unrelated donor, the risk of recurrence was lower, and the 5-year leukemia-free and overall survival rates were similar (37% vs 39% and 38% vs 39%, respectively). A similar trend toward comparable outcomes in ALL from matched, unrelated donors and sibling donors also was observed in other studies.[71,77] However, treatment-related mortality of matched, unrelated transplantations rose significantly with older age, mismatched donors, and T-cell depletion.

Outcomes remain poor for older patients, especially those aged >60 years. Although patients still may benefit from the graft-versus-leukemia effect, transplantation-related mortality can be substantial. In recent years, the results from allogeneic transplantations with reduced-intensity conditioning regimens have been published in small series of patients.[78,79] Low transplantation-related mortality rates and overall survival rates at 3 years of up to 30% have been reported, suggesting that reduced-intensity conditioning transplantation is a promising modality for selected patients in whom regular conditioning regimens are not indicated.

Acute Lymphoblastic Leukemia in Adolescents and Young Adults

AYAs constitute a particular group of patients who find themselves sandwiched between younger children and adults and who may be referred to either pediatric or adult oncologists. Several recent studies comparing the outcome of AYAs on pediatric and adult protocols demonstrated improved survival for AYAs who were treated by pediatric groups, findings that triggered intense interest in the differences with respect to ALL biology, protocol designs,

and social aspects.[80-82] In a retrospective comparison of 321 AYAs between ages 16 years and 20 years who were treated on either a Childrens' Cancer Group (CCG) study or a CALGB study, there was no difference in remission rates (90% in both groups), but 7-year event-free and overall survival were significantly superior for the CCG-treated patients (63% vs 34% and 67% vs 46%, respectively; $P < .001$).[80] Reasons that may explain this difference include 1) different protocol designs (higher doses of nonmyelosuppressive drugs, early and more frequent CNS prophylaxis, and oral dexamethasone instead of prednisone in the CCG protocol); 2) biologic differences, such as the distribution of prognostically relevant cytogenetic abnormalities; 3) different practice patterns between pediatric and adult oncologists (with the former presumably more experienced); and 4) a complex web of social factors (support systems, compliance) in favor of AYAs under the care of pediatric oncologists. The recently published Group for Research on Adult Acute Lymphoblastic Leukemia GRAALL-2003 study, a pediatric-inspired therapy program for adults, came to similar conclusions: The incidence of chemotherapy-related deaths, the complete remission rate, and the event-free and overall survival rates in that study compared favorably with those reported from previous adult programs, especially for patients aged <45 years.[83] Currently, prospective trials are planned with a focus on AYAs and the possibility of extending the pediatric approach to adult patients up to ages 40 years to 50 years.[84,85]

Philadelphia Chromosome-Positive Acute Lymphoblastic Leukemia

Ph-positive ALL is a particularly important subtype primarily for adults and, thus, is emphasized separately. It is a disease with a historically dismal prognosis in which HSCT has provided the only chance for a cure.[86] Conversely, 1 of the most significant advances in subtype-specific therapy in the form of TKIs also has effected Ph-positive ALL in recent years and has opened whole new perspectives of how to treat these patients. Even single-agent TKIs (eg, imatinib) can produce response rates of 20% to 30%, but response durations are short. Combinations of TKIs with chemotherapy have been more promising.[87-89] In the imatinib and hyper-CVAD combination, imatinib 600 mg was given daily for 14 days with the induction cycle and then continuously thereafter until the dose was increased to 800 mg for indefinite maintenance therapy.[87] Of 54 patients (median age, 51 years; range, 17-84 years), 93% achieved complete remission with a median time to response of 21 days. The molecular response rate by nested PCR was 52%. Sixteen patients proceeded to allogeneic HSCT within a median of 5 months from the start of therapy. It is noteworthy that survival at 3 years was equal whether or not patients underwent HSCT (63% vs 56%). With 3-year overall survival rates of 55% versus 15% ($P < .001$) for hyper-CVAD without imatinib, the TKI/chemotherapy combination was more active than hyper-CVAD alone. Imatinib appeared to be most effective when it was started early during induction and given concurrently with and subsequent to induction and consolidation rather than alternating with chemotherapy.[90] TKI therapy combined with low-intensity therapy (vincristine, steroids) may be of benefit for elderly and frail patients who are not good candidates for more aggressive therapy and in whom both induction mortality and death in complete remission occur more frequently.[91]

Dasatinib and nilotinib are more potent than imatinib, are active against most imatinib-resistant kinase domain mutations, and have produced responses in patients with imatinib-resistant Ph-positive ALL.[92,93] Experience in frontline Ph-positive ALL is limited to early studies with dasatinib in which rapid hematologic clearance of bone marrow blasts and residual disease with a manageable toxicity profile was observed in most patients.[94,95]

Despite high remission rates and favorable disease-free survival data, the long-term success rate of TKIs with or without chemotherapy combinations remains to be defined. Although the threshold to use alternative donor sources (matched unrelated donor, mismatched transplantations) for HSCT has been raised, matched sibling HSCT, when available, remains valid.

Acute Lymphoblastic Leukemia Recurrence

Salvage therapy in ALL remains challenging, because the long-term prognosis is generally poor.[96,97] More favorable long-term leukemia-free survival rates of 14% to 43% are achieved with allogeneic HSCT; however, the lack of a donor, comorbidities, and uncontrollable disease are frequent impediments.[98] Conventional treatments mainly mirror variations of drug combinations used in several induction protocols: 1) combinations of vincristine, steroids, and anthracyclines; 2) asparaginase and methotrexate; or 3) high-dose cytarabine. Given the poor results reported in patients with recurrent ALL and the lack of effective agents, several new drugs with different mechanisms of action are being investigated in clinical trials (Table 4).[99,100] Among those, nelarabine is a soluble prodrug

Table 4. Additional Drugs in Acute Lymphoblastic Leukemia Therapy

Category/Drug
Nucleoside analogs
Clofarabine
Nelarabine (T-cell)
Forodesine
Liposomal and pegylated compounds
Liposomal vincristine
Liposomal doxorubicin
Liposomal annamycin
Liposomal cytarabine
Pegasparaginase
Monoclonal antibodies
Rituximab
Ofatumumab
Alemtuzumab
Epratuzumab
Gemtuzumab ozogamicin
CAT-3888 (BL22): Anti-CD22 immunotoxin
MoAb216: Human IgM MoAb
Antifolates
Pemetrexed
DNA methyltransferase inhibitors and histone deacetylase inhibitors
LBH589
PDX101
Azacitidine
Decitabine
Tyrosine kinase inhibitors
Imatinib
Dasatinib
Nilotinib
mTOR inhibitors
RAD001
Microtubule-destabilizing agents
ENMD-1198
Fms-like tyrosine kinase-3 inhibitors
Lestaurtinib
Midostaruin
Tandutinib
Sunitinib malate

MoAb indicates monoclonal antibody; IgM, immunoglobulin M; mTOR, mammalian target of rapamycin.

of 9-β-D-arabinofuranosylguanine (ara-G) that has activity predominantly in recurrent T-lineage lymphoid malignancies and was approved by the US Food and Drug Administration (FDA) for this indication in October 2005. Response rates of 33% and 41% have been achieved in a group of 121 children and 39 adults with recurrent T-lineage leukemia/lymphoma, respectively.[101,102] The median overall survival in the adult group was 20 weeks. Neurotoxicity is the major adverse event of nelarabine, which is both dose-dependent and schedule-dependent and can be limited by administration every other day rather than daily. Clofarabine, another new nucleoside analogue, is approved by the FDA for the treatment of pediatric patients with recurrent or refractory ALL who have received at least 2 prior regimens of chemotherapy based on promising results from a phase 2 trial.[103] Studies of this drug alone and in combination (eg, with cyclophosphamide) are ongoing in adult ALL. Given the heterogeneity and complexity of ALL in recurrence, a single drug alone is unlikely to make a crucial difference. Rather, it is the painstaking endeavor of filtering out the most prominent agents in early studies and learning how to apply those agents best in combination programs that eventually may shift the tide.

Conclusions

ALL is a success story for pediatric cancer therapy. Yet, for adults, durable benefits remain mostly elusive. This is not for a lack of powerful induction programs. Complete remission rates already are uniformly high and are unlikely to improve to any significant degree. The challenge is to maintain the remissions and, for those who do develop recurrent disease, to provide effective salvage therapy. Thus, the 2 issues in need of a solution are: 1) a lack of new and active drugs and 2) proper patient selection for transplantation (ie, early as opposed to later). With regard to the lack of effective drugs, there are obvious exceptions, such as TKIs in Ph-positive ALL and nelarabine in T-lineage ALL but far more is needed. The debate about transplantation will be ongoing. Although the MRC/ECOG study provides important data, the conclusions should not be considered definitive, because the study is based on a definition of standard risk that is rather restricted and would benefit from the addition of MRD measurements. Therapy for ALL will remain complex, and progress ultimately will depend on effective crossbreeding between drug development, understanding of ALL biology, and sophistication of prognostic systems.

CONFLICT OF INTEREST DISCLOSURES

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