Adult Acute Lymphoblastic Leukemia

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CME Activity

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Abstract

Conventional cytotoxic chemotherapy used to treat acute lymphoblastic leukemia (ALL) results in high cure rates in pediatric patients but is suboptimal in the treatment of adult patients. The 5-year overall survival is approximately 90% in children and 30% to 40% in adults and elderly patients. Adults with ALL tend to have higher risk factors at diagnosis, more comorbidities, and increasing age that often requires dose reductions. Major advancements have been made in redefining the pathologic classification of ALL, identifying new cytogenetic-molecular abnormalities, and developing novel targeted agents in order to improve survival. The addition of new monoclonal antibodies and tyrosine kinase inhibitors to conventional chemotherapy in the frontline setting has resulted in increased rates of complete remission and overall survival. These new developments are changing the treatment of adult ALL from a "one therapy fits all" approach to individualized treatment based on patient's cytogenetic and molecular profile.

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Acute lymphoblastic leukemia (ALL) is a hematologic malignancy propagated by impaired differentiation, proliferation, and accumulation of lymphoid progenitor cells in the bone marrow and/or extramedullary sites. Although ALL occurs predominantly in children, it is adult ALL that is more challenging to treat. Treatment of adult ALL is largely modeled after the multiagent chemotherapy regimen utilized in pediatric ALL designed 5 decades ago. This regimen consists of induction, consolidation, and maintenance therapy and central nervous system (CNS) prophylaxis that has produced a

cure rate of 90% and 60% in children and adolescents, respectively.[1,2] Unfortunately, the treatment success of pediatric ALL has not been mimicked in adult ALL. Despite high rates of complete remission (CR) (80%-90%) in adult ALL, the cure rates are only 40% to 50% because of relapses.[3-5] The 5-year overall survival (OS) is approximately 90% in children and 30% to 40% in adults and elderly patients.[4] This problem may be attributed to adults harboring higher-risk features at diagnosis, increased comorbidities, and the development of chemotherapy resistance after relapse. The need for improvement in adult ALL outcomes has led to major advancements in drug development, reassessment of risk stratification, and better knowledge of disease pathogenesis. The incorporation of targeted therapies in the frontline and salvage settings has improved survival compared with that of conventional chemotherapy in adult ALL. However, the goal is to further optimize treatment regimens so it can one day be revered as a success story similar to pediatric ALL.

EPIDEMIOLOGY AND ETIOLOGY

ALL has a bimodal distribution with the first peak occurring in individuals around 5 years of age and the second peak at around 50 years of age. It is mainly considered a pediatric leukemia with 80% of cases occurring in children and 20% occurring in adults.[4-7] The median age at diagnosis is 14 years, and approximately 60% of patients are diagnosed at younger than 20 years of age, 25% at around 45 years of age, and 11% at around 65 years of age.[8] ALL is relatively uncommon during late childhood, adolescence, and young adulthood. According to the Surveillance, Epidemiology, and End Results program database, the estimated annual incidence in the United States was approximately 6590 new cases and 1430 deaths in 2016.[9] The age-adjusted incidence rate in the United States is 1.7 per 100,000 men and women per year.

The etiology of ALL is largely unknown. Less than 5% of cases can be attributed to genetic syndromes such as Down syndrome, Klinefelter syndrome, Fanconi anemia, Bloom syndrome, ataxia-telangiectasia, and Nijmegen breakdown syndrome.[10-16] Other risk factors include increasing age (>70 years) and exposure to radiation. There has also been an association between Epstein-Barr virus in mature B-cell ALL, human T-lymphotropic virus type 1 in adult T-cell leukemia/lymphoma, and human immunodeficiency virus in lymphoproliferative disorders.[17,18] The fetal environment is thought to play a vital role in the development of pediatric ALL.[19] The hypothesis is that as cells proliferate during fetal development, random alterations occur creating a preleukemic clone. As exposure to the pathogen increases during early childhood, there is an increase in lymphoid proliferation leading to ALL.

CLINICAL PRESENTATION AND LABORATORY ABNORMALITIES

The clinical presentation of ALL is nonspecific, and thus, patients can present with an array of ailments such as "B symptoms" (ie, fever, unexpected weight loss, night sweats), infection, easy bruising/bleeding, dyspnea, and fatigue due to low blood cell counts.[8] Patients may exhibit petechiae, pallor, and ecchymosis on physical examination, but children may present with only joint pain.[19]

Approximately 20% of patients will have leukemic infiltration in the spleen and/or liver leading to splenomegaly and/or hepatomegaly.[8] Other extramedullary presentations can occur in the testis, skin, or mediastinum (specifically in T-cell ALL).[19,20] Patients with mature B-cell ALL (Burkitt leukemia) may present with an abdominal mass and spontaneous tumor lysis syndrome due to high disease burden. The CNS is one of the sanctuary sites of ALL, and approximately 5% to 8% of patients initially present with CNS involvement such as cranial neuropathies and meningeal infiltration.[2,4,19] Patients with Burkitt-like ALL may experience chin numbness as a result of cranial nerve involvement.[19,20]

DIAGNOSTIC EVALUATION

The diagnosis of ALL requires the presence of 20% or more lymphoblasts in the bone marrow.[8] Further assessment by flow cytometry, morphological studies, immunophenotyping, and cytogenetic testing is important. Historically, the diagnosis of ALL was based on the French-American-British morphological criteria that described 3 subtypes of

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ALL (L1, L2, and L3) based on cell size, cytoplasm, nucleoli vacuolation, and basophilia.[21] Because of this system's lack of prognostic value, a classification based on immunophenotypic characteristics of ALL blasts was proposed in 1995.[22] In 2008, the World Health Organization proposed a composite classification based on the combined cytogenetic and immunophenotypic characteristics of the blasts.[23-25] In the 2016 revision, ALL is classified into B-lymphoblastic and T-lymphoblastic categories with 2 new provisional genetic entities added (B-ALL with intrachromosomal amplification of chromosome 21 and B-ALL with translocations involving tyrosine kinases or cytokine receptors ["*BCR-ABL1*- like ALL"] [for expansion of gene symbols, see www.genenames.org]).[26] B-cell ALL comprises approximately 90% of cases in children and 75% in adults while T-cell ALL comprises the remaining cases.[24-26]

B-cell ALL blasts are almost always positive for CD19, cytoplasmic CD79a, and cytoplasmic CD22.[24-26] The B-cell lymphoblasts are positive for CD10, surface CD22, *PAX5*, and *TdT* in most cases, while CD20 and CD34 expressions are variable; CD45 may be absent. The degree of differentiation of B-lineage lymphoblasts has clinical and genetic correlates. In the earliest stage (early precursor B-cell ALL), the blasts express CD19, cytoplasmic CD79a, cytoplasmic CD22, and nuclear *TdT* but are negative for CD10. In the intermediate stage, the blasts express CD10. In mature precursor B-cell ALL or pre−B-cell ALL, the blasts express cytoplasmic μ chains, CD10, CD19, CD79a, CD22, and CD20 in 45% of the cases, but rarely surface light chains. The leukemic variant of Burkitt lymphoma is now regarded as a mature B-cell neoplasm with membrane IgM and light chain expression with other genetic findings. The leukemic variant also has a high frequency of CD20 expression (>80%).[24-28]

T-cell ALL is known for its CD3 positivity and variable expression of CD2, CD5, CD1a, CD7, CD52, and *TdT*.[29,30] This lineage is also divided into 3 subgroups: early thymic precursor T-cell ALL (ETP-ALL) (∼20%), cortical/thymic ALL (∼50%-60%), and medullary/mature ALL (∼20%). Early thymic precursor T-cell ALL accounts for only 2% of cases of ALL, but outcome is relatively poor even with treatment. Patients with ETP-ALL are positive for CD7 and negative for CD1a and CD8. They have weak expression of CD5 and have at least one myeloid or stem cell marker (C12, CD11b, CD34, CD117, CD33, CD65, HLA-DR).[8,26] Gene mutations such as *IDH1*, *IDH2*, *DNMT3A*, *NRAS/KRAS*, and *FLT3* commonly occur with ETP-ALL.

Cytogenetic analysis is important in characterizing individual prognostic subsets and providing an insight into the molecular events causing leukemia (Table 1).[4,31-34] The disparity in outcomes of children and adults with ALL is partially due to the incidence of favorable and unfavorable karyotypes. Most recently, use of molecular studies such as microarray profiling, DNA copy number analysis, and next-generation sequencing has helped unmask several new mutations in ALL that may lead to aberrant pathway activation and cell survival.[35,36]

TABLE 1. Molecular and Cytogenetic Abnormalities in ALL[a]

Type	Cytogenetic abnormality	Frequency in adults (%)	Genes involved
Hyperdiploid	NA	2-15	*BCR-ABL1*
Hypodiploid	NA	5-10	NA
Ph-positive	t(9;22)(q34;q11)	15-25	*BCR-ABL1*
Others	del(11)(q22-23)	25-30[b]	*ATM*
	t(17;19)	<5	*E2A-HLF*
	t(4;11), t(9;11)	5-10	*MLL*
	t(7;9)(q34;q32)	<1	*TAL2*
	del(9)(q21-22)	6-30	*p15, p16*
	del(13)(q14)	<5	*miR15, miR16*
	t(1;19)	<5	*E2A-PBX1*
	t(1;14)(p32;q11)	10-15[d]	*TAL1*
	t(12;21)(p12;q22)	<1[c]	*TEL-AML1*
	t(10;14)(q24;q11)	5-10	*HOX11*
	t(5;14)(q35;q32)	1	*HOX11L2*
	del(6q), t(6;12)	5	NA
	+8	10-12	NA
	t(8;14), t(8;22)	5	*C-MYC*
	del(5q)	<2	NA
	del(7p)	5-10	NA

Data from references.[4,31-34]

[a]ALL = acute lymphoblastic leukemia; NA = not applicable; Ph = Philadelphia chromosome. For expansion of gene symbols, see www.genenames.org.

[b]Determined by loss of heterozygosity.

[c]Measured by polymerase chain reaction.

[d]Incidence is <10% in T-cell ALL.

Because most ALL studies have been performed in pediatric patients, there is a scarcity of reported genomic data for adults. Philadelphia chromosome (Ph)−like ALL is a recently described entity with a poor prognosis. It occurs in approximately 10% of children and up to 30% of young adults with ALL.[36,37] It has a genetic profile similar to *BCR-ABL1* ALL without the expressed fusion protein t(9;22) (q34;q11.2).[37,38] In 80% of cases, patients have deletions of crucial transcription factors (*IKZF1*, early B-cell factor, paired box 5, *VPREB1*, and transcription factor 3) intrinsic to B-cell hematopoiesis.[39] Kinase activating alterations are seen in 90% of patients with Ph-like ALL. Some of the genetic rearrangements seen in Ph-like ALL involve *ABL1* and *ABL2*, colony-stimulating factor 1 receptor, *CRLF2*, erythropoietin receptor, *JAK2*, *PDGFB*, *TSLP*, or tyrosine kinase 2. Other sequence mutations involved include *FLT3*, interleukin 7 receptor, or *SH2B3*. Rearrangements of the *CRLF2* gene constitute 50% of mutations, leading to an overexpression of its protein and subsequent downstream signaling through *JAK* kinases.[40-43] A list of newer genetic determinants is presented in Table 2.

In addition to Ph-like ALL, ETP-ALL, minimal residual disease (MRD) positivity, *IKZF1* mutation, translocation (4;11), hypodiploidy, increasing age, and complex karyotype (≥5 chromosome abnormalities) are also associated with poor prognosis.

TREATMENT

The structure of adult ALL treatment is similar to that for pediatric ALL; the chemotherapy consists of induction, consolidation, and long-term maintenance therapy along with CNS prophylaxis interwoven during the first year of treatment. The purpose of this multidrug treatment approach is to eradicate the disease and restore normal hematopoiesis, provide prophylaxis to "sanctuary sites," and prevent an upsurge of resistant clones that may lead to relapse.[19]

Induction Therapy

The goal of induction therapy is to induce CR by eradicating leukemic cells in the bone marrow. Drugs like vincristine, anthracycline (eg, daunorubicin or doxorubicin), corticosteroids (eg, prednisone or dexamethasone), with or without L-asparaginase and/or

TABLE 2. Genetic Determinants in ALL[a]

Type of ALL	Cytogenetic abnormality	Protein	Genes involved	Comments
T cell	NA	NA	*RAS/PTEN*, *FBW7*, *PICALM-MLLT10*, *NUP214-ABL1* fusion, *MLL*, *SET-NUP214* fusion, *PTPN2*, *NOTCH1*, *BCL11B*, *JAK1*,*PHF6*, *IL7R*, *EML-ABL1*	Poor outcomes with *RAS/PTEN* and *JAK1* Favorable outcomes with *FBW7* (∼20%) and/or *NOTCH1* (>60%)
B cell	Near-hypodiploid	NA	*FLT3*, *NF1*, *KRAS*, and *NRAS*	Occurs in 70% of cases
	Ph-like	NA	NUP214-ABL1, in-frame fusions of EBF1-PDGFRB *IKZF1* deletions, *BCR-JAK2* or *STRN3-JAK2*, rearrangements/mutations in *CRLF2*, cryptic *IGH-EPOR* rearrangements IGH-*CRLF2*	Occurs in 15% of cases. Utilization of TKIs and/or *JAK2* inhibitors and mTOR is possible
	Hyperdiploid	NT5C2	*TP53* mutations, *CREBBP*, *NT5C2* mutations	Occurs in 6% of cases
	Positive *BCR/ABL* (Ph+)	Ikaros	*IKZF1*	Outcome is poor. Occurs in approximately 80% of Ph+ cases
	Low-hypodiploid	NA	*TP53* disruptions, *IKZF2*, *CDKN2A/B* locus deletion	Occurs in 91% of cases

Data from references.[4,40-43]

[a]ALL = acute lymphoblastic leukemia; NA = not applicable; Ph+ = Philadelphia chromosome−positive. For expansion of gene symbols, see www.genenames.org.

cyclophosphamide are highly active in ALL and are the backbone of most induction regimens. Some randomized clinical trials have found that dexamethasone significantly reduces the risk of isolated CNS relapse and improves event-free survival (EFS) in comparison to prednisone because dexamethasone is able to achieve higher drug concentrations in the cerebrospinal fluid than prednisone.[44,45] However, toxicities such as myopathy, neuropsychiatric adverse events (AEs), and an increased risk of mortality reported with dexamethasone must be noted. Because data on OS with dexamethasone in comparison to prednisone is lacking, the superiority of one corticosteroid over the other has not been established.

There are several ALL induction regimens that are largely based on the same fundamental drugs with differences in 1 or 2 drugs and their administration schedule. Some notable regimens such as the Berlin-Frankfurt-Münster (BFM)/Children's Oncology Group and Cancer and Leukemia Group B protocols differ only by the addition of cyclophosphamide. The addition of L-asparaginase in pediatric and adolescent and young adult (AYA) ALL regimens has led to improved outcomes. Conversely, in adult ALL, asparaginase has been identified as too toxic and is believed to have contributed to poorer outcomes. In the UKALL14, a randomized trial, 91 adults (median age, 47 years; range, 25-65 years), were treated with pegylated (peg) asparaginase 1000 IU/m^2 intravenously (IV), on days 4 and 18 during induction.[46] Although the CR was 66%, there was a high rate of induction mortality (19.8%) and hepatotoxicity (55.6%) among the adult population. Because the risk outweighed the benefit, peg-asparaginase was omitted in patients 40 years of age or older.

Hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (HCVAD) is one of the most widely used adult ALL treatment regimens. It consists of 8 alternating treatment cycles labeled as "A" and "B." Part A of the regimen contains hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone.[2,47,48] Part B contains high-dose methotrexate and cytarabine. For CNS prophylaxis, intrathecal (IT) chemotherapy is given twice during each cycle for at least 4 cycles. Cranial radiation is an alternative option for those who present with CNS leukemia at diagnosis. Hematopoietic growth factors (eg, granulocyte colony-stimulating factor) are given after each cycle to hasten bone marrow recovery in order to retain dose intensity and prevent any delay in therapy. This regimen yields a 5-year CR duration (CRD) of 53% and OS of 60%.[49] The CR rate is 100% with a median follow-up of 88 months. Patients younger than 40 years of age are reported to have a higher 5-year OS than patients older than 60 years of age (51% and 17%, respectively). Patients who achieve CR after first induction (CR1) receive consolidation chemotherapy or allogeneic hematopoietic stem cell transplant (alloSCT) based on risk stratification and the feasibility of obtaining a donor.

Consolidation Therapy. The purpose of consolidation therapy is to eliminate any residual leukemic cells remaining after induction therapy. The drugs utilized are often similar to those used in the induction phase and vary according to the treatment regimen selected and the patient population being treated. For instance, L-asparaginase and 6-mercaptopurine may be incorporated in the treatment of children with ALL. Consolidation therapy is followed by a prolonged maintenance phase.

Maintenance Therapy. The intent of maintenance therapy is to prevent relapse and prolong remission. This phase consists of daily 6-mercaptopurine, weekly methotrexate, monthly vincristine, and monthly pulses of prednisone (POMP) administered for a period of 2 to 3 years, beyond which it has not had any benefit.[19,50-52] This regimen is referred to as "DOMP" if dexamethasone is substituted for prednisone. The omission or reduction of the maintenance phase is associated with worse outcomes except in patients with mature B-cell ALL (eg, non-Hodgkin lymphoma, Burkitt lymphoma). Patients with mature B-cell ALL have early long-term remissions, and relapse after 1 year is rare; thus, maintenance therapy is not necessary.[53] Historically, patients with Ph-positive ALL who were in CR1 and had an available donor underwent alloSCT instead of receiving maintenance therapy. However, with

the incorporation of tyrosine kinase inhibitors (TKIs) in the maintenance phase of Ph-positive ALL treatment, alloSCT has become an option instead of a necessity.

Central Nervous System Prophylaxis. The CNS is one of the sanctuary sites of ALL, and thus, CNS prophylaxis is embedded in the treatment regimens to prevent CNS disease and/or CNS relapse. Primary CNS involvement at diagnosis is rare (<10%) but may be as high as 75% after a year without prophylaxis.[2,47] High-dose methotrexate and cytarabine also penetrate the CNS, but they are unable to eradicate all leukemic cells in the brain. Therefore, IT chemotherapy must be given. The addition of IT methotrexate and cytarabine reduces the incidence of CNS relapse by 4%. Standard-risk patients receive a total of 8 IT chemotherapy doses, while high-risk patients such as those with Ph-positive ALL and Burkitt lymphoma receive 12 and 16 doses, respectively.[2] Treatment with craniospinal radiation is a less favorable option because it leads to neurologic and cognitive dysfunction as well as secondary cancer. St. Jude Children's Research Hospital conducted a study on secondary malignant brain neoplasms after treatment of childhood ALL.[54] With a median follow-up of 16 years, 21 patients had development of brain tumors of various types. The risk factors for development of secondary brain tumors were dose-dependent cranial irradiation, cumulative radiation therapy, and CNS involvement at diagnosis, highlighting the limitations of cranial radiation especially with increasing cumulative doses.

The diagnosis of CNS disease requires the presence of more than 5 white blood cells per microliter in the cerebrospinal fluid with those cells being identified as lymphoblasts in the CNS differential diagnosis.[55] Outcomes of CNS disease in adults, especially CNS relapse, are poor and treatment is challenging. The median OS is 6 months, and cure is often restricted to patients who undergo alloSCT. Central nervous system–directed treatment with craniospinal radiation, triple IT chemotherapy (methotrexate, cytarabine, and a corticosteroid), thiotepa, and liposomal cytarabine can be used. These patients often have leukoencephalopathy, headache, nausea, and neurologic dysfunction due to the site of disease and cumulative toxicity from treatment.

Stem Cell Transplant

Historically, high-risk patients were defined as those with Ph-positive ALL, high white blood cell count ($>30 \times 10^9$/L for B-cell ALL or 100×10^9/L for T-cell ALL), mixed-lineage leukemia gene [eg, t(4;11)], and hypodiploidy.[4,56] These patients would receive an alloSCT in place of consolidation therapy once they achieved CR1. Recently, Ph-like ALL and ETP-ALL have been found to have poor outcomes, and therefore, patients with either diagnosis are considered to be in the high-risk category.[35] In addition, a new risk-adapted approach that considers the patient's risk status over time has been incorporated. This approach helps identify patients who would benefit most from a transplant.

The emergence of MRD as a prognostic marker has redefined risk stratification in ALL across all age groups, serving as a crucial factor in determining outcomes of alloSCT. Bassan et al measured MRD status at various time points after achieving CR to determine optimal treatment strategies in adult ALL.[57] If patients had MRD positive disease despite being in CR at the end of the consolidation phase, they were restratified as high-risk and received alloSCT instead of maintenance therapy. The maintenance phase was reserved for patients without MRD positive disease, and such patients were found to have significantly higher 5-year OS than those with MRD positivity (75% vs 33%, respectively; P=.001). Minimal residual disease was also a significant prognostic marker in the relapse setting (hazard ratio [HR], 5.22). Furthermore, Dhédin et al found that patients with poor MRD response after induction therapy had longer relapse-free survival (RFS) after an alloSCT.[58] Conversely, outcomes did not differ between standard chemotherapy alone and alloSCT among high-risk patients with MRD. These findings highlight the importance of utilizing MRD response as a criterion for selecting patients who may benefit the most from a transplant.

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Minimal Residual Disease

The presence of MRD after induction therapy is an independent marker of poor prognosis signifying chemotherapy-refractory disease.[57-64] The time from treatment initiation to relapse is approximately 8 months despite continued chemotherapy.[59] Of note, MRD is assessed by multiparameter flow cytometry (FCM) in the United States and by polymerase chain reaction in Europe.

Gökbuget et al studied the significance of an alloSCT in 120 patients with MRD after first consolidation (week 16).[59] Patients with MRD who received alloSCT had a significantly higher 5-year continuous CR than patients with MRD who did not receive an alloSCT after CR1 (66% vs 12%, respectively; $P<.0001$). The disease-free survival (DFS) rates were similar in both groups.

The PETHEMA ALL-AR-03 (Programa Español de Tratamientos en Hematología Treatment of High Risk Adult Acute Lymphoblastic Leukemia) trial conducted a multivariate analysis of 326 adolescents and adults with high-risk Ph-negative ALL.[60] This study found that poor MRD clearance, defined as 1×10^{-3} blasts or more after induction therapy and 5×10^{-4} blasts or more after consolidation therapy identified by FCM, was the only significant prognostic marker for DFS and OS. Identification of MRD also serves as a therapeutic target for newer monoclonal antibodies and chimeric antigen receptor–modified T cells (CAR-Ts).

Frontline Therapy

Treatment of Adult and AYA Patients. Retrospective studies have found that pediatric ALL treatment regimens are superior to adult regimens (except HCVAD) in treating AYA patients (aged 15-39 years).[65] Some pediatric regimens can be effective in adults (≥40 years), but CRs are not as high. Pediatric regimens are based on intensive and nonmyelosuppressive agents such as vincristine, peg-asparaginase, and dexamethasone.

In the US Intergroup study, 318 AYA patients (aged 17-39 years; median age, 24 years) were treated with a pediatric-inspired regimen (Children's Oncology Group AALL0232).[66] With a median follow-up of 28 months, the 2-year EFS and OS were 66% and 78%, respectively. Of note, patients with Ph-like ALL (28%) had lower 2-year EFS rates compared with those without the Ph-like signature (52% vs 81%; $P=.04$).

The Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) studied 225 patients up to 60 years of age who were treated with a pediatric-inspired regimen and compared them with a historical control group of 712 adults treated with an adult regimen (Leucémie Aigüe Lymphoblastique de l'Adulte [LALA-94]).[67] They found a statistically significant improvement in the study group for CR (93.5%), EFS (55%), and OS (60%). However, in a subgroup analysis, superior outcomes were seen only in patients younger than 45 years. In patients between the ages of 40 and 60, there was a 23% cumulative incidence of chemotherapy-related deaths, indicating that pediatric-type regimens in adult ALL may marginally improve cure rates at the expense of potentially deadly toxicities.

Recently, DeAngleo et al conducted a phase 2 study utilizing a pediatric regimen (Dana-Farber Cancer Institute Childhood ALL Consortium Protocol 05-01) with dose-intensified peg-asparaginase in adults (aged 18-50 years) with ALL.[68,69] Initially, *Escherichia coli*–derived asparaginase was utilized during the induction and consolidation phases, but several patients had development of hyperbilirubinemia. Subsequently, the study was amended, and the dose of peg-asparaginase was reduced to 2000 IU/m^2 given every 3 weeks during consolidation therapy. With a median follow-up of 42 months, 90 of 110 patients achieved CR and the 3-year DFS and OS rates were 73% and 75%, respectively. The most notable AEs were allergic reactions (n=14), osteonecrosis (n=12), thrombosis/embolism (n=13), grade 3 to 4 neutropenic infections (n=32), and pancreatitis occurring in 4 patients after induction therapy. Similar to other studies, older patients did poorly, thus limiting the use of peg-asparaginase to younger patients.

The MD Anderson Cancer Center (MDACC) conducted a study spanning over 8 years (2006-2014) involving 106 AYA patients (median age, 22 years) treated with a pediatric regimen (augmented BFM) and compared the results with those from 102 AYA patients (median age, 27 years) treated

with HCVAD with or without rituximab.[49] The outcomes were similar in both groups, with CR rates of 93% in the augmented BFM group and 98% in the HCVAD group. The 5-year CRD rates (~50%) and OS (60%) were similar in both groups. Because of the inclusion of peg-asparaginase, the augmented BFM regimen had a significantly higher incidence of AEs such as hypofibrinogenemia, pancreatitis, severe allergies, thrombosis, and elevated liver enzyme levels. Conversely, myelosuppression was commonly seen with HCVAD. This study proves that AYA patients can be treated with an adult regimen such as HCVAD and have outcomes similar to those of a pediatric regimen.

Treatment of Elderly Patients. Elderly patients with ALL (≥60 years of age) have a high rate of induction mortality (42%) with standard chemotherapeutic regimens.[70,71] Approximately one-third die of chemotherapy-related complications or relapse after achieving CR.[71] The median survival is 15 months, and only 20% are alive at 3 years, primarily due to poor tolerance of intensive chemotherapy requiring dose reductions that directly lead to ineffective drug delivery. Therefore, reducing the intensity of chemotherapy while preserving efficacy may improve outcomes in elderly patients with ALL. In the prospective GMALL (German Multicenter Study Group for Adult ALL) study, 268 elderly patients were treated with BFM.[72] The CR and 5-year OS rates were 76% and 23%, respectively; however, the early death rate was 14% and the mortality rate for patients with CR was 6%. Patients younger than 75 years who had a good performance status fared better, with a higher CR rate (86%), lower early death rate (10%), and 3-year survival rate of 36%.

Inotuzumab ozogamicin is a humanized monoclonal antibody targeting CD22-expressing cells. This monoclonal antibody is covalently linked to calicheamicin, which is a cytotoxin that causes breakage in double-stranded DNA.[73] In a phase 2 study, 34 patients with newly diagnosed Ph-negative ALL were treated with inotuzumab plus mini-HCVD, a low-intensity chemotherapy (hyperfractionated cyclophosphamide and dexamethasone at 50% dose reduction, vincristine no anthracycline, 75% dose reduction of methotrexate, and 83% dose reduction of cytarabine).[73] Inotuzumab was administered during the first 4 courses of mini-HVCD, one dose of 1.3 mg/m^2 during course 1 followed by 1 mg/m^2 once during courses 2, 3, and 4. The median age was 69 years (range, 60-79 years), and median follow-up was 23 months. The objective response rate was 97% (CR rate of 80%). All patients in CR also achieved negative MRD status. The 2-year CRD and OS rates were 81% and 64%, respectively. Furthermore, the 2-year survival rates were higher with mini-HCVD plus inotuzumab than historical rituximab with or without HCVAD (70% vs 38%, respectively). Veno-occlusive disease (VOD) was observed in 11% of patients, and other notable grade 3 to 4 toxicities included hyperbilirubinemia (24%), liver function test result elevation (21%), prolonged thrombocytopenia (79%), and infection during induction and consolidation therapy (52% vs 73%). Overall, this study documented the superiority of inotuzumab plus mini-HCVD over standard rituximab with or without HCVAD as a front-line treatment of ALL in elderly patients.

Treatment of Mature B-Cell and Burkitt ALL. Approximately 80% of patients with mature B-cell ALL express CD20, which previously was associated with a poor prognosis. Rituximab is a chimeric human/mouse monoclonal antibody specific to CD20. It was initially evaluated in lymphoid malignancies such as non-Hodgkin lymphoma and then subsequently in chronic lymphocytic leukemia and ALL.[74] The addition of rituximab to standard chemotherapy in non-Hodgkin lymphoma has yielded OS rates greater than 20%, and in chronic lymphocytic leukemia, it has improved 3-year OS from 83% to 87% (P=.012).[75] In a phase 2 study, the addition of rituximab to HCVAD in mature B-cell ALL significantly improved 3-year survival from 53% to 89%.[76] Hoelzer et al conducted one of the largest multicenter prospective trials in adult patients with Burkitt lymphoma/leukemia and found benefits of adding rituximab to induction therapy.[77] Rituximab was given at 375 mg/m^2 before each cycle and 2 times in the maintenance phase for a total of 8 doses.

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The addition of rituximab significantly improved CR, 5-year progression-free survival (PFS), and OS rates (88%, 71%, and 80%, respectively). Age was a predictive factor for outcome; the 5-year survival rates for adolescents, adults, and elderly patients were 90%, 84%, and 62%, respectively.

In the GRAALL-Lysa study, Ribrag et al compared chemotherapy alone to chemotherapy plus rituximab.[78] Rituximab was administered twice during the first 2 courses on day 1 and day 6 for a total of 4 doses. The 3-year EFS (75% vs 62%; P=.024) and OS (83% vs 70%; P=.001) rates with rituximab plus chemotherapy were significantly better than chemotherapy alone without increasing the incidence of AEs.

Rituximab was also evaluated in combination with low-intensity chemotherapy. A pilot study was conducted to assess the efficacy of rituximab in combination with etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin in adult patients with Burkitt lymphoma.[79] Patients mainly had low- to intermediate-risk disease, and the combination was well tolerated and highly effective. The freedom from progression and OS rates were both greater than 90%. This combination is currently being studied in mature B-cell ALL.

Treatment of Precursor B-Cell ALL

Rituximab. Approximately 30% to 50% of precursor lymphoblasts express CD20 antigen.[28] Thomas et al evaluated the addition of rituximab to modified HCVAD in pre−B-cell ALL.[80] Rituximab was given for 2 doses during each of the first 4 cycles of intensive chemotherapy (total of 8 doses) and then incorporated into late intensification cycles (months 6 and 18 of maintenance therapy). The modifications made to HCVAD included risk-adapted IT chemotherapy for CNS prophylaxis, the maintenance phase was prolonged by 6 months, and early anthracycline intensification was administered. The CR, 3-year CRD, and 3-year OS rates were 95%, 60%, and 50%, respectively. Patients younger than 60 years had significantly higher 3-year CRD and OS rates with rituximab plus modified HCVAD (70% vs 38%, P<.001; and 75% vs 47%, P=.003, respectively). The GMALL also found an increase in survival and 5-year remission duration in patients younger than 55 years when rituximab was added to standard chemotherapy.[81,82] The incidence of MRD negativity improved with rituximab as well.

Recently, the pivotal multicenter randomized trial GRAALL-R 2005 reported the benefit of rituximab in the treatment of CD20-positive precursor B-cell ALL.[83] Between 2006 and 2014, 220 patients from 56 centers were randomized to intensive chemotherapy with or without rituximab. Rituximab was administered at 375 mg/m^2 IV for a total of 16 to 18 infusions. Patients with high-risk disease who achieved CR1 and had an available donor were offered alloSCT. With a median follow-up of 30 months, the chemotherapy plus rituximab group had a significantly higher EFS rate (primary end point) than the group that did not receive rituximab (65% vs 52%, respectively; P=.038). The OS rate was not significantly different (71% with rituximab vs 64% without; P=.095). However, after censoring for alloSCT, better OS was observed in patients who received rituximab. Overall, the combination treatment was well tolerated and was associated with longer OS and EFS.

Ofatumumab. Ofatumumab is a second-generation anti-CD20 monoclonal antibody currently approved for the management of relapsed/refractory (R/R) chronic lymphocytic leukemia.[84] The binding site of ofatumumab is distinctly different from that of rituximab. Ofatumumab is also more potent than rituximab because of its stronger binding to B cells with a slower dissociation rate. Furthermore, ofatumumab has notable activity after rituximab exposure. In an ongoing phase 2 study, 48 patients with pre−B-cell ALL and CD20 expression above 1% were treated with HCVAD-ofatumumab.[85] Ofatumumab, 2 g, was administered on day 1 and day 11 during the first 4 courses of induction therapy and during course 6 and 18 of intensification therapy. The CR was 98%, and the MRD negativity rate was 93% (62% at CR). With a median follow-up of 24 months, the 3-year CRD and OS rates were 75% and 67%, respectively. Overall, the treatment was well tolerated.

Treatment of Ph-Positive ALL. The incidence of Ph-positive ALL increases with

patient age. It occurs in approximately 2% to 5% of cases of childhood ALL and in 20% to 40% of cases in adult and elderly patients.[8,86,87] Historically, patients with Ph-positive ALL had a poor prognosis, with 1-year survival of approximately 10%; alloSCT was the only hope for cure.[87,88] The addition of *BCR-ABL1* TKIs to chemotherapy has substantially improved outcomes in these patients.

Several studies have reported improved outcomes with imatinib, a first-generation TKI, in combination with chemotherapy followed by alloSCT.[89-94] Thomas et al first studied imatinib plus HCVAD in patients with newly diagnosed or minimally treated Ph-positive ALL.[91,92] Imatinib was administered on days 1 through 14 during induction therapy and then continuously thereafter.[92] Patients received either alloSCT following CR1 if feasible or maintenance therapy. The median follow-up was 77 months, and the 3-year CRD and OS rates were significantly higher with combination therapy than with HCVAD alone (68% vs 24% and 54% vs 15%, respectively; $P<.001$). Schultz et al studied the efficacy of imatinib in combination with intensive chemotherapy in children and adolescents with Ph-positive ALL.[93] The toxicities were then compared to Ph-negative ALL patients who received intensive chemotherapy without imatinib. Imatinib was administered at 340 mg/m^2 per day, and the exposure and duration were increased with each cohort (cohort 5, n=50). The results revealed that continuous imatinib exposure led to significantly higher outcomes. The 3-year EFS rate was 80% compared to the historical 3-year EFS rate of 35% ($P<.0001$). There were no added toxicities observed with imatinib, and in fact, higher imatinib dosing led to better outcomes.

In effort to maintain efficacy and reduce the toxicity of intensive chemotherapy, Chalandon et al conducted a large study (GRAAPH-2005) with high-dose imatinib plus reduced-intensity chemotherapy.[94] The 268 patients aged 18 to 59 years were randomized to 2 treatment arms. In arm A, patients received high-dose imatinib (800 mg/d, days 1-28) with weekly vincristine and dexamethasone, and in arm B, patients received standard imatinib (800 mg/d, days 1-14) with HCVAD. Both arms received similar consolidation regimens with a goal of alloSCT if a donor was available or an autologous stem cell transplant if the patient did not have a donor but had a major molecular response (MMR). Of note, imatinib was administered in an intermittent fashion. Reduced-intensity chemotherapy had a significantly higher CR rate (98.5% vs 91%; $P=.006$) and lower incidence of death (0.7% vs 6.7%; $P=.01$) during induction therapy. The MMR rate (66% vs 64%) and 5-year OS rate (37.1% vs 45.6%; $P=.37$) were similar in both arms. There was a significant benefit in OS ($P=.02$) and RFS ($P=.036$) among patients who underwent alloSCT. There was no difference in MMR rate among patients who received alloSCT or autologous stem cell transplant. Furthermore, the benefit of transplant was mainly observed in patients who did not achieve a molecular remission with induction/consolidation chemotherapy.

Although imatinib in combination with chemotherapy has been proven to increase favorable outcomes, some patients may be resistant to initial treatment or may relapse after treatment.[95] Furthermore, CNS relapses have been reported with imatinib because of its low cerebrospinal fluid concentrations in the CNS.[96] Dasatinib, a second-generation TKI, was originally developed in patients with chronic myeloid leukemia with intolerance to and/or treatment failure with imatinib. Dasatinib is more potent than imatinib against the BCR-ABL1 protein, and it also inhibits the *SRC* family of kinases.[97] The *SRC* kinases contribute substantially to the pathophysiology of Ph-positive ALL. Dasatinib has also been reported to cross the blood-brain barrier.[98] The effectiveness of dasatinib in achieving long-term remission was first assessed in a single-center study conducted at MDACC.[99] In that study, 72 patients received dasatinib plus HCVAD and underwent alloSCT in CR1 if a donor was available. Patients without donors received maintenance therapy for 2 years with dasatinib, vincristine, and corticosteroids, followed by dasatinib indefinitely. The CR, complete cytogenetic response (CCyR) after first cycle, and complete molecular response (CMR) rates were 96%, 83%, and 65%, respectively. Twenty-two patients proceeded with alloSCT (12 in CR1 and 10 in CR after second induction [CR2]).

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The 5-year DFS and OS rates were 44% and 46%, respectively. The grade 3/4 AEs included bleeding, pericardial/pleural effusions, and elevated transaminase levels. Subsequently, Ravandi et al conducted a multicenter study assessing the efficacy of dasatinib in combination with HCVAD in 94 patients (aged 18-60 years) with newly diagnosed Ph-positive ALL.[100] With a median follow-up of 26 months, 88% had achieved a CR or partial CR. The 3-year EFS and OS rates were 54% and 71%, respectively.

Investigators in Europe assessed a lower-intensity chemotherapy regimen in combination with dasatinib. Rousselot et al studied dasatinib with low-intensity chemotherapy in the EWALL-Ph-01 (European Working Group on Adult ALL study number 01 for Ph[+] ALL) trial.[101] Patients 55 years or older with newly diagnosed Ph-positive ALL were treated with dasatinib plus low-intensity chemotherapy. During induction therapy, patients received 140 mg/d of dasatinib with vincristine and dexamethasone and 100 mg/d of dasatinib with methotrexate and asparaginase alternating with cytarabine during consolidation therapy. In the maintenance phase, patients received dasatinib plus POMP. The CR rate was 96%, and the 5-year OS and RFS rates were 36% and 28%, respectively. Of note, 36 patients experienced relapse, and 75% of these patients had a T315I mutation. Chiaretti et al conducted a multicenter trial (Gruppo Italiano Malattie EMatologiche dell'Adulto LAL 1509) with a similar concept.[102] Sixty patients with a median age of 42 years received corticosteroids for 35 days (day −6 to day 31) plus dasatinib, 140 mg/d, from day 1 through day 84. In patients who achieved CMR, dasatinib was continued infinitely. Patients who were not in CMR at 3 months received chemotherapy followed by alloSCT, if feasible. Near the end of 85 days, 97% of patients were in complete hematologic remission and 18.6% were in CMR. Among the 46 patients who did not achieve CMR, there were 12 deaths and 14 relapses. The 3-year DFS and OS rates were 48.9% and 58.3%, respectively. In a multivariate analysis, the achievement of CMR was an independent predictor of better survival.

Nilotinib, a second-generation TKI, was also studied as a frontline treatment in combination with low-intensity chemotherapy in elderly (≥55 years) patients with Ph-positive ALL.[103] In the EWALL-Ph-02 study, nilotinib was administered at 400 mg twice daily during induction and then continuously through consolidation and maintenance therapy. With a median follow-up of 7 months, 97% of patients achieved CR, and the overall CMR rate was 42% after consolidation and 30% after induction therapy. The combination was also well tolerated.

Despite the major improvement in outcomes, relapses are common, the acquisition of the T315I kinase domain mutation being one of the main reasons.[104] Ponatinib is a potent third-generation TKI that has the ability to suppress nearly all *BCR-ABL1* kinase domain mutations, especially T315I clone, thus overcoming resistance seen in first- and second-generation TKIs.[104-106] In chronic myeloid leukemia patients with T315I mutation, ponatinib had a CCyR rate of 53% in patients who failed multiple TKIs.[106] As a result, ponatinib was assessed in the management of Ph-positive ALL.

In a phase 2 single-arm trial, 52 patients with Ph-positive ALL received ponatinib plus HCVAD.[107] Initially, ponatinib was given at 45 mg/d, but the protocol was amended after the occurrence of 2 fatal myocardial events. Thereafter, ponatinib was given at 45 mg/d for 14 days during induction therapy, followed by 30 mg continuously starting at the second cycle and 15 mg/d once a CMR was achieved. After the dose adjustment, no further vascular events were reported. The CR, CCyR, MMR, and CMR rates were 100%, 91%, 96%, and 79%, respectively. With a median follow-up of 3 years, the CRD and OS rates were 79% and 82%, respectively. The grade 3/4 toxicities included infections during induction therapy, elevated levels on liver function tests, thrombotic events, myocardial infarction, pancreatitis, and rash.

Ponatinib was then compared to dasatinib in combination with HCVAD.[108] With 109 patients, the propensity score analysis revealed no difference in CR and MRD. However, the 3-year OS and EFS rates were significantly higher in the ponatinib vs the dasatinib group (83% vs 60%, P=.041 and 73% vs 50%, P=.035, respectively). These findings indicate the superiority of ponatinib over dasatinib in the treatment of Ph-positive ALL.

In the pre-TKI era, alloSCT in CR1 was the only way to improve outcomes. Currently, the need for alloSCT in CR1 is debatable. The recent use of MRD has raised questions about the optimal timing of an alloSCT in these patients. Ravandi et al studied the predictive value of MRD by quantitative polymerase chain reaction and FCM at various time points.[109] The study population was 122 patients with Ph-positive ALL treated with chemotherapy plus TKI who did not receive an alloSCT in CR1. Improvement in survival was strongly associated with achieving MMR at 3, 6, 9, and 12 months (P=.02, P=.04, P=.05, and P=.01, respectively). This study highlighted the importance of MRD monitoring in patients with Ph-positive ALL and its ability to identify patients who may benefit from an alloSCT. Furthermore, additional analysis revealed that the best outcome was observed in patients who achieved CMR within 3 months of therapy; the 4-year OS rates were 66%, 43%, and 32% in patients with 3-month CMR, MMR, and less than MMR, respectively.[110] Therefore, patients in CMR may not need to undergo transplant in CR1.

The best results with TKIs are seen when they are added early to Ph-positive ALL treatment and taken concurrently on a continuous basis as compared to intermittent or pulsed administrations.[111] Therefore, it is imperative to initiate TKI theray upon confirmation of Ph positivity, and it should be administered over a prolonged continuous period.

Treatment of T-Cell ALL. T-cell ALL is less common than B-cell ALL among children and adults.[4,8] In general, the treatment of T-cell ALL is similar to that for B-cell ALL because the National Comprehensive Cancer Network guidelines makes no distinctions between their treatments.[8] In comparison to B-cell ALL, outcomes of T-cell ALL are highly variable and are often offset by a 50% relapse rate if treated with conventional chemotherapy such as HCVAD.[8,29] Most of the oncogenic processes in T-cell ALL involve constitutive activation of *NOTCH1* signaling (50%-60%) with its highest frequency in the thymic subgroup of T-cell ALL.[8,112] Other mutations in T-cell ALL include *JAK3* (12%), *FBXW7* (10%), *WT1* (10%), *PHF6* (11%), and *BCL11B* (10%). There are also epigenetic mutations in *DNMT3A,* polycomb repressive complex 2, *JAK/STAT* (*JAK1*, *JAK2*, *JAK3*, *IL7R*), and ribosomal processes (*RPL10*, *RPL5*).

Early thymic precursor T-cell ALL accounts for 10% of cases of adult T-cell ALL. It has a higher rate of remission failure and 10-year relapse than typical T-cell ALL (72% vs 10%, respectively).[29] Therefore, early recognition of ETP-ALL and effective treatment is crucial. The mutation profile lacks *NOTCH1* and *CDKN1/2* expression but contains genetic mutations involving *FAT1*, *FAT3*, *FLT3*, *DNM2* and *DNMT3A*, *IDH1*, *IDH2*, and *NRAS/KRAS*, which may serve as therapeutic targets.[26,29,112] Early thymic precursor T-cell ALL is known to activate mutations in genes that govern the cytokine receptor and RAS signaling (67%) as well as inactivate lesions that interfere with hematopoiesis (58%) and histone modifying genes (48%). This mutation profile is similar to that of myeloid neoplasms, and hence, addition of myeloid-based therapies may improve ETP-ALL outcomes.

Nelarabine is a T-cell–specific purine nucleoside analogue that is catabolized to arabinosylguanine triphosphate.[113,114] T cells appear to accumulate arabinosylguanine triphosphate at higher levels, and once incorporated into the DNA, arabinosylguanine triphosphate leads to inhibition of DNA synthesis and eventually apoptosis. Currently, nelarabine is approved for the treatment of R/R T-cell lymphoma/leukemia following at least 2 chemotherapy regimens. Frontline T-cell ALL treatment with nelarabine in combination with HCVAD is being evaluated. At the MDACC, nelarabine plus HCVAD was given to 48 patients (median age, 38 years) with de novo T-cell ALL and 36 patients with T-cell lymphoblastic lymphoma .[115] Nelarabine was administered at a dose of 650 mg/m^2 IV daily for 5 days after cycles 4 and 5 of HCVAD and then with POMP maintenance therapy. The CR rate was 93% with no difference between T-cell ALL and T-cell lymphoblastic lymphoma (89% vs 94%, respectively). The 3-year OS rate was 63% with a median follow-up of 41 months. Patients with ETP-ALL had a shorter 3-year OS in comparison to those with thymic and mature T-cell ALL (45%, 78%, and 100%, respectively). The most common grade 3/4 AEs were infection, gastrointestinal tract

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intolerance (nausea, vomiting, and diarrhea), pancytopenia, and elevated transaminase levels. Patients with ETP-ALL should be considered for alloSCT after CR1.

Salvage Treatment

Although adults have high initial CR, approximately 40% to 50% experience relapse, with 66% being in the high-risk category.[116-118] The overall response rates (ORRs) after relapse are low and vary between 25% and 50% based on the duration of first remission. In the R/R setting, alloSCT offers less than a 30% chance for cure, but less than 10% of patients are able to undergo this procedure. Immunotherapy in the form of monoclonal antibodies targeting CD19 and CD22 have allowed for better management of R/R ALL. Currently, the monoclonal antibodies with the most mature data and promising results are blinatumomab and inotuzumab ozogamicin.

Blinatumomab. Blinatumomab is a bispecific T-cell—engaging antibody that links the CD3 T-cell receptor to CD19 on B cells.[119] This synapse causes release of inflammatory cytokines, production of cytolytic proteins, and proliferation of T cells that results in lysis of CD19 B cells. It was initially studied in non-Hodgkin lymphoma and chronic lymphocytic leukemia at doses of 0.75 to 13 $\mu g/m^2$ IV over 2 to 4 hours for up to 3 times a week.[120] This type of administration failed to produce any objective response, but it did result in severe neurologic symptoms such as seizures, aphasia, tremors, and disorientation leading to discontinuation of treatment in some patients. As a consequence, in a phase 1 study of R/R non-Hodgkin lymphoma, blinatumomab was administered as a continuous infusion and dose-escalated to a target dose of 60 $\mu g/m^2$ per day.[121] The reason for continuous infusion was to increase efficacy and prolong drug exposure over time without the toxic peaks seen with an intermittent dosing schedule. At the target dose, the ORR was 69%.

Minimal Residual Disease. As previously mentioned, MRD positivity confers poor prognosis because of the high incidence of systemic relapse. Blinatumomab was initially studied in patients with morphological or hematologic CR with persistent or reappearing MRD positivity. The efficacy of blinatumomab was assessed in 21 patients with MRD-positive ALL.[122] Of the 20 evaluable patients, 16 (80%) became MRD negative after the first cycle of therapy. Subsequently, 9 patients underwent alloSCT and had favorable outcomes similar to those patients who did not undergo transplant. The relapses reported occurred within 7 months of blinatumomab initiation. At a median follow-up of 33 months, approximately 60% of patients remained in CR. This efficacy was confirmed in a pivotal open-label multicenter trial (BLAST). Gökbuget et al assessed single-agent blinatumomab in 116 patients with ALL in CR but with MRD positivity.[123] Most patients had undergone 3 or more courses of chemotherapy, and 35% or more were in CR2. Blinatumomab was given at 15 $\mu g/m^2$ per day continuous IV infusion (CIVI) for 28 days every 6 weeks for 4 cycles. Approximately 78% achieved MRD negativity after 1 cycle and 80% after 4 cycles. With a median follow-up of 29.5 months, the median OS was approximately 36 months and RFS was 19 months. There was no difference in OS and RFS between patients who received an alloSCT in CR1 and those who did not (HR, 1.39 [P=.37] and 0.89 [P=.73], respectively).

Relapsed and Refractory Disease. Blinatumomab was also studied in adult patients with Ph-negative R/R ALL. A pivotal phase 2 multicenter study was conducted in 189 patients.[124] These patients were treated with 9 μg/d CIVI for the first week and then 28 μg/d CIVI during weeks 2 through 4 in the first cycle and subsequent cycles. Patients received up to 4 cycles after the first induction cycle. The CR was 43% with 82% of patients achieving MRD negativity. The median survival was 6.1 months. Based on these results, blinatumomab was approved by the US Food and Drug Administration in December 2014 for patients with R/R ALL.

A phase 3 randomized trial (TOWER study) compared blinatumomab to investigators' choice of chemotherapy in patients with R/R ALL.[125] More than 400 patients with R/R Ph-negative ALL were randomized to either blinatumomab (n=271) or standard care

chemotherapy (n=134). The ORRs were 45% and 30%, respectively (*P*=.007). Molecular remission rates among responders, defined as the presence of less than 10^{-4} blasts in the first 12 weeks, were 75% and 48%, respectively. Blinatumomab prolonged the primary study end point of OS; the median OS was 7.7 months (range, 5.6-9.6 months) with blinatumomab and 4.0 months (range, 2.9-5.3 months) with standard care chemotherapy, respectively (*P*=.012; HR, 0.71).

Blinatumomab was also evaluated in the phase 2 ALCANTARA trial in patients with R/R Ph-positive ALL.[126] Blinatumomab was given at the standard dose for up to 5 cycles in 45 patients, 36% of whom achieved CR or partial hematologic response after the first 2 cycles. Of the responders, 86% had complete MRD response. With a median follow-up of 9 months, the median RFS and OS were 6.7 months and 7.1 months, respectively.

Most of the blinatumomab AEs are mild to moderate and occur during the first cycle. Thus, patients begin with a lower dose (9 μg/d) for the first 7 days and are monitored closely in the hospital. Common AEs include chills, pyrexia, constitutional symptoms, and reversible neurologic events such as tremors, seizures, aphasia, and ataxia.[119] In order to minimize these adverse effects, all patients are premedicated with dexamethasone during day 1 of the first cycle and the first day of any dose escalation (Table 3).[124-127]

Inotuzumab Ozogamicin. Inotuzumab ozogamicin, a monoclonal antibody against CD22, was initially studied in non-Hodgkin lymphoma at a maximally tolerated dose of 1.8 mg/m^2 IV given over 3 to 4 weeks.[128] The ORR was 39%, and the most common reversible AE was thrombocytopenia. As a result, a phase 2 study was conducted in R/R ALL starting at 1.3 mg/m^2 IV in the first 3 patients and then a subsequent dose increase of 1.8 mg/m^2 IV every 3-4 weeks.[129] The study enrolled 49 patients, and 73% had received 2 or more salvage regimens before treatment with inotuzumab. The ORR was 57% after a median of 2 cycles, and the median survival was approximately 5 months. Nearly 50% of patients were able to undergo alloSCT. Common AEs included fever and hypotension following the infusion. Notable serious toxicities included a high incidence of VOD (n=5, 23%), mainly observed in patients who received double alkylators as part of their pretransplant conditioning. In order to minimize toxicities without compromising efficacy and based on the pharmacokinetic and pharmacodynamic data, inotuzumab was administered on a weekly basis at 0.8 mg/m^2 IV on day 1 followed by 0.5 mg/m^2 IV on days 8 and 15 every 3 to 4 weeks.[130] This study yielded an ORR similar to that of the monthly regimen (59% vs 57%, respectively) with a median survival between 5-7.3 months. However, weekly administration of inotuzumab resulted in fewer AEs, including lower rates of VOD. Advani et al also conducted a phase 2 study of inotuzumab in heavily pretreated patients with R/R ALL.[131] The median OS was 7.4 months with a remission rate of 65.7%. These

TABLE 3. Blinatumomab in Relapsed/Refractory ALL[a,b]

	Ph-negative			Ph-positive
Parameters	Pivotal phase 2 (N=36)	Confirmatory phase 2 (N=189)	Phase 3 (TOWER trial) (N=405)	Pivotal phase 2 (ALCANTRA trial) (N=45)
CR/CRh	25 (69)	81 (43)	NR	16 (36)
RFS (mo), median	7.6	5.9	NR	6.7
OS (mo), median	9.8	6.1	7.7	7.1
Salvage 1	11	35	91	NR
Salvage ≥2	10	151	66	NR

[a]ALL = acute lymphoblastic leukemia; CR = complete response; CRh = CR with incomplete hematologic recovery; NR = not reported; OS = overall survival; Ph = Philadelphia chromosome; RFS = relapse-free survival.

[b]Data are presented as No. (percentage) of patients unless indicated otherwise.

Data from references.[124-127]

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encouraging results led to an international study comparing weekly inotuzumab to standard ALL chemotherapy in the first or second salvage therapy setting.[132] The objective response rates were 81% and 33%, respectively. Among responders, the MRD negativity rates were 78% and 28%, respectively. The median PFS was 5.0 vs 1.8 months, respectively ($P<.001$). The median OS was 7.7 vs 6.7 months ($P=.02$; HR, 0.77). The 2-year survival rates were 23% and 10%, respectively.

Inotuzumab was combined with dose-reduced HCVAD, known as low-intensity HCVD, for 8 courses in the salvage setting.[133] Inotuzumab was given on day 3 of each of the first 4 cycles. The addition of rituximab was allowed if patients had 20% or more CD20 expression. The treatment cycle was 3 to 4 weeks long, and patients who responded received POMP maintenance therapy for 1 year followed with vincristine and corticosteroids for 2 years if the patient did not undergo alloSCT. In the 52 patients treated, the objective response rate was 77% (53% CR) and the MRD negativity rate was 82%. The median survival was 11 months. The 2-year PFS and OS rates were 60% and 32%, respectively. For patients receiving their first salvage therapy, the 2-year OS rate was 50%. When compared to single inotuzumab therapy in similar patients, the median survivals were better (6 vs 11 months, respectively), favoring the combination (Table 4).

The results with blinatumomab and inotuzumab are encouraging. Studies incorporating targeted agents early in ALL treatment will hopefully improve survival through early molecular remission and reduced relapse rates.

Chimeric Antigen Receptor–Modified T Cells. Chimeric antigen receptor–modified T cells are genetically modified autologous T lymphocytes that are engineered to express binding sites of specific antibodies, such as a receptor against CD19 leading to the death of CD19-expressing cells.[134,135] T cells are harnessed from a patient's own immune system and modified to express various receptors necessary to target the destruction of the malignant cells. First-generation CAR-Ts were studied in B-cell malignancies such as CD20 and CD19, but these cells lacked antitumor activity. Subsequently, second-and third-generation CAR-Ts were created with costimulatory domains that improved their expansion and persistence in vivo. In the fourth-generation CAR-Ts, cytokines or costimulatory ligands were added to increase the expansion and longevity. Since then, there have been several modifications to optimize cytotoxic activity while minimizing toxicity.

Park et al are conducting a study with CAR-Ts in patients with R/R ALL.[136] Currently, 46 patients are enrolled, 45 of whom are evaluable for response. The median age is 45 years (range, 22-74 years). Most patients had 3 previous types of therapy, and approximately 30% had Ph-positive ALL and previous alloSCT. Half of the patients had

TABLE 4. Summary of Clinical Trials With Inotuzumab in Relapsed/Refractory ALL

Parameters	Single dose	Weekly dose	CR 39 patients (35.8%) CRi 49 patients (45%)		INO + mini-HCVD
INO dose/schedule	1.8 mg/m^2 on day 1 every 3-4 wk	0.8 mg/m^2 on day 1, 0.5 mg/m^2 on days 8 and 15	0.8 mg/m^2 on day 1, 0.5 mg/m^2 on days 8 and 15		1.8 mg/m^2 in cycle 1 followed by 1.3 mg/m^2 for remaining courses on day 3 of first 4 courses
Results			INO	SC	
ORR	57%	66%	81%	33%	77%
CR	18%	31%	35.8%		53%
CRp	10%/29%	34%	45%		19%
OS (mo)	5	7.4	7.7	6.7	11

Data from references.[129,131-133]

ALL = acute lymphoblastic leukemia; CR = complete response; CRp = complete response with incomplete count recovery; HCVD = hyperfractionated cyclophosphamide, vincristine, and dexamethasone; INO = inotuzumab; NR = not reported; ORR = overall response rate; OS = overall survival; SC = standard care.

active disease, while the other half were in marrow CR. Complete remission was attained in 36 patients (84%). Only 35 of the 36 patients in CR were evaluated for MRD of which 29 patients (83%) became MRD negative. Seven patients were disease free beyond 1 year; the median survival is about 11 months for those in CR with MRD negativity. Survival did not differ if patients received an alloSCT after CAR-T therapy, but MRD negativity was a strong predicator of better outcomes.

Outcomes of CAR-T therapy at the University of Pennsylvania and The Children's Hospital of Philadelphia have also been reported.[137] In this study, 59 children with R/R ALL have received treatment, and 93% experienced CR with a 1-year OS rate of 79%. With a median follow-up of 12 months, RFS is 55%, and 34 patients are still in CR. Relapse has occurred in 20 patients and 13 of them are CD19 negative. Cytokine release syndrome occurred in 88% of the patients, but all recovered.

The use of dexamethasone and tocilizumab are interventions thought to blunt the cytokine release syndrome effect of CAR-Ts. As a result, their appropriate use and time frame are still debatable. Treatment with CAR-Ts is a highly innovative strategy for R/R ALL, and there are several ongoing trials assessing their optimal clinical use.

TREATMENT APPROACH

A bone marrow examination must be performed to confirm the diagnosis of ALL. In addition, a complete immunophenotypic, cytogenetic, and molecular panel should be conducted because it is crucial for risk stratification and to determine targetable mutations. This will help determine the most optimal treatment regimen.

Adolescents and Young Adults

For AYA patients, pediatric regimens have been found to substantially improve OS without notable toxicity. In the GRAALL study, patients younger than 45 years of age were noted to have better OS with pediatric-inspired regimens. Conversely, at the MDACC, the CR rate and 3-year CRD were similar between augmented BFM and rituximab-HCVAD, and thus either regimen would be effective. If the patient is CD20 positive, adding rituximab or ofatumumab to chemotherapy is highly recommended.

Elderly Patients

Patients 60 years of age or older have a high rate of toxicities when treated with intensive chemotherapy. In order to maintain efficacy and reduce toxicity, low-intensity HCVD plus inotuzumab was studied. This low-intensity chemotherapy was well tolerated and produced a 2-year OS of 70%, with 75% of patients becoming MRD negative after the first cycle.

Mature B-Cell ALL

In mature B-cell ALL, the addition of rituximab has drastically improved outcomes, as evidenced by several studies quoting OS rates of 50% to 80%. For patients with Burkitt leukemia who have low- or intermediate-risk disease, dose-adjusted etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin is a promising treatment with PFS and OS rates of up to 100%. In addition, due to a high risk of CNS relapse, patients with Burkitt leukemia should receive a total of 16 doses of IT chemotherapy as prophylaxis.

Pre–B-Cell ALL

Data from the MDACC, German multicenter study group for adult ALL, and the landmark GRAALL-R 2005 studies have revealed improvement in survival and an increase in EFS rate with the addition of rituximab to conventional chemotherapy. As a result, rituximab should be added to chemotherapy in patients with pre–B-cell ALL with positive CD20 expression. Newer generations of anti-CD20 monoclonal antibodies are being tested.

T-Cell ALL

Patients with T-cell ALL have achieved CR in 93% of cases with a 5-year OS rate of 66%. Patients with mature T-cell ALL have a better outcomes than those with ETP-ALL. In patients with ETP-ALL, alloSCT should be considered after CR1.

Ph-Positive ALL

The treatment and outcomes of Ph-positive ALL have changed considerably with the incorporation of TKIs, which has now become

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standard care. Among the TKIs studied in Ph-positive ALL, ponatinib has had a higher response rate and deeper molecular response. Choice of the most appropriate TKI should always be based on patient-specific factors, mutations, and the drug's adverse effect profile in mind. All TKIs should be given on a daily and continuous basis because this regimen is more effective than intermittent dosing. It is also important that these patients receive a total of 12 doses of IT chemotherapy to prevent and reduce the risk of CNS relapse.

Stem Cell Transplant

Several studies have provided better guidance and insight regarding which patients benefit from alloSCT vs prolonged maintenance therapy following CR1. For high-risk young adults with ALL who have an available donor, an alloSCT in CR1 is appropriate. In standard-risk patients, MRD status should be utilized to help develop a treatment strategy. Patients who are MRD positive can be restratified to a high-risk category and would benefit from an alloSCT in CR1. However, with the recent availability of blinatumomab, a bispecific monoclonal antibody targeted against C19 and CD3 cells, the treatment approach to MRD-positive ALL may drastically change. Studies have found that patients in hematologic and morphological CR but with persistent or reappearing MRD positivity treated with blinatumomab can achieve MRD negativity as quickly as the first cycle. Furthermore, outcomes appear to be similar in those with MRD positivity who undergo alloSCT versus those who receive blinatumomab. Thus, the treatment strategy for MRD-positive patients may change to blinatumomab alone or at least 1 or 2 cycles of blinatumomab followed by alloSCT. In addition to MRD status, gene expression profiling and immunophenotypic techniques are important in identifying poor prognostic subgroups of ALL such as patients with ETP-ALL and Ph-like ALL who may benefit from alloSCT in CR1. Otherwise, alloSCT should be offered to all patients in CR2.

CONCLUSION

Major progress has been made in revising prognostic factors, understanding the impact of MRD, and the development of novel targeted therapies for adult patients with ALL. The addition of rituximab to conventional chemotherapy in the treatment of B-cell ALL has substantially improved survival. The incorporation of TKIs in the treatment of Ph-positive ALL has drastically improved outcomes, but their role after transplant is still to be determined. Blinatumomab and inotuzumab have marked activity in the R/R setting. Furthermore, inotuzumab in combination with low-intensity chemotherapy increases ORR and improves outcomes in elderly patients, who historically have had high rates of death due to toxicity from conventional chemotherapy. Currently, several questions remain as to the best combination of drugs and the best sequence of administration. The monoclonal antibodies can possibly be incorporated during the initial stages of treatment to induce higher rates of MRD negativity and to potentially reduce the need for overall intensive or maintenance chemotherapy. As current trials advance into their last stages and data matures, the role and sequence of these novel agents may be redefined. This new data may translate into improvement of cure rates in adult ALL to the level achieved in pediatric populations.

Abbreviations and Acronyms: **AE** = adverse event; **ALL** = acute lymphoblastic leukemia; **alloSCT** = allogeneic hematopoietic stem cell transplant; **AYA** = adolescent and young adult; **BFM** = Berlin-Frankfurt-Münster; **CAR-T** = chimeric antigen receptor—modified T cell; **CCyR** = complete cytogenetic response; **CIVI** = continuous intravenous infusion; **CMR** = complete molecular response; **CNS** = central nervous system; **CR** = complete remission; **CR1** = CR after first induction; **CR2** = CR after second induction; **CRD** = CR duration; **DFS** = disease-free survival; **EFS** = event-free survival; **ETP** = early thymic precursor T-cell; **FCM** = multiparameter flow cytometry; **GMALL** = German Multicenter Study Group for Adult ALL; **GRAALL** = Group for Research on Adult Acute Lymphoblastic Leukemia; **HCVAD** = hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone; **HCVD** = hyperfractionated cyclophosphamide, vincristine, and dexamethasone; **HR** = hazard ratio; **IT** = intrathecal; **IV** = intravenously; **MDACC** = MD Anderson Cancer Center; **MMR** = major molecular response; **MRD** = minimal residual disease; **ORR** = overall response rate; **OS** = overall survival; **peg** = pegylated; **Ph** = Philadelphia chromosome; **PFS** = progression-free survival; **POMP** = 6-mercaptopurine, vincristine, methotrexate, and prednisone; **RFS** = relapse-free survival; **R/R** = relapsed/refractory; **TKI** = tyrosine kinase inhibitor; **VOD** = veno-occlusive disease

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The Symposium on Neoplastic Hematology and Medical Oncology will continue in an upcoming issue.

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