

Treatment of Acute Lymphoblastic Leukemia in Older Adults: Now and the Future

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Abstract: Acute lymphoblastic leukemia (ALL) is an uncommon disease with poor outcomes in older patients. Although intensive chemotherapy can induce complete responses in older patients, the mortality rate is unacceptably high. The 5-year survival rate for patients achieving a remission ranges from 17% to 23%. ALL is usually more aggressive in older patients, and these patients' reduced functional capacity renders them less able to tolerate treatment. The need for less-intensive, more-efficient treatment modalities in this population of frail and high-risk patients is evident. Clinicians should strongly consider treatment in clinical trials for their older patients. If such trials are not available on site, physicians should refer older patients to tertiary centers for possible enrollment in a study. Significant advances have been made in the past decade toward understanding the biology of ALL and in developing novel therapeutic agents. Blinatumomab, inotuzumab ozogamicin, and newer-generation tyrosine kinase inhibitors appear to be promising agents. Clinical studies show remarkable results with these agents, either alone or in combination with low-dose chemotherapy. Now that clinical trials are being designed with less-intensive treatment regimens and broad entry criteria, older age is less likely to be an exclusionary factor. However, clinical trials that enroll older patients with ALL should include detailed documentation of their underlying comorbidities, cognitive function, and performance status.

Introduction

Acute lymphoblastic leukemia (ALL) is a rare disease that accounted for 0.4% of all new cancer cases and 11% of new leukemia cases in the United States in 2016.¹ In that year, approximately 12% of patients in whom ALL was diagnosed were 65 years of age or older (Figure). Because the life expectancy of the general population is increasing, it has been estimated that the incidence of leukemia in people 65 years of age and older will increase by 68% from 2010 to 2030.² Older people with a diagnosis of ALL do not experience the excellent outcomes seen in children and young adolescents, and those aged 55 to 60 years or older have been reported to have the

Keywords

Acute lymphoblastic leukemia, blinatumomab, inotuzumab ozogamicin, older adults, tyrosine kinase inhibitors

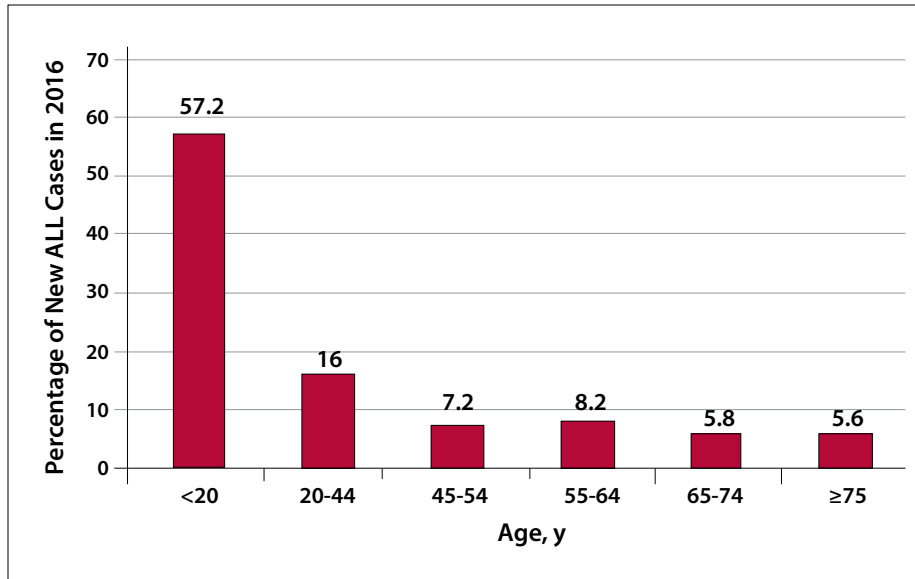


Figure. Distribution of cases of acute lymphoblastic leukemia (ALL) in 2016 by age groups.

Source: SEER stat fact sheets: acute lymphocytic leukemia (ALL). National Cancer Institute.¹

worst outcomes. Elderly patients do not respond as well as younger adults to chemotherapy, and they die earlier in the disease course. The need for less-intensive, more-efficient treatment modalities in this population of frail, high-risk patients is evident. This review summarizes the literature regarding outcomes in older patients with ALL treated with conventional chemotherapies, and the results of newly emerging treatment modalities are discussed. *Older* or *elderly* patients are defined as those 60 years of age and older, which is consistent with most of the available literature. Some series define elderly patients as those who are 55 years old and older or 65 years old and older.

Biological and Clinical Characteristics of Older Patients

The definition of an older adult is somewhat arbitrary. Because no precise age cutoff defines older patients with ALL, categorization should be based on multiple factors beyond chronologic age. Both patient-related factors and the biological characteristics of the disease should be considered when treatment decisions are made.

A significant amount of evidence indicates that the biological and clinical features of ALL differ between older and younger patients. Bulky lymphadenopathy, mediastinal involvement, and high white blood cell counts appear to be more common in younger patients than in older ones.³ Elderly patients are more likely to be female and to have a worse performance status.⁴ Approximately two-thirds of older patients may have underlying comorbidities; the German Multicenter Study Group for Adult ALL (GMALL) reported high rates of diabetes mellitus (46%), vascular disease (18%), congestive heart failure

(15%), and chronic pulmonary disease (12%) among elderly patients.⁵ Among older patients with ALL, 8% to 16% had a prior diagnosis of another malignancy.^{3,5} A systematic evaluation of each patient's comorbidities and functional status is essential to the decision of whether to administer intensive chemotherapy because a weak candidate is more likely to die during induction or early in the course of treatment. A complete geriatric assessment by the treating physician often is not feasible owing to time constraints in daily practice. One practical solution is the use of a standardized, comprehensive self-report system as part of the initial evaluation of every older patient with ALL.⁶

The baseline immunophenotypes and cytogenetic profiles of young and older patients with ALL have been studied extensively and found to be relatively different. One study compared the immunophenotypes of patients who were at least 60 years old ($n=69$) with those of adults younger than 60 years ($n=309$). The researchers found that leukemic blasts exhibited the B-cell immunophenotype in 89% of the older patients vs 66% of the younger patients ($P<.001$).³ In contrast, the T-cell immunophenotype was observed in 29% of the younger adults and 8% of the older adults ($P<.001$). The immunophenotype was unclassified in 5% of the younger patients and 3% of the older patients. Myeloid markers were coexpressed more commonly in older patients. The Philadelphia (Ph) chromosome, $t(9;22)(q34;q11)$, was the most common adverse cytogenetic abnormality in the elderly patients; its incidence increased with age, up to 24%, and reached a plateau by the age of 40 to 49 years.⁴ The median age of patients with another poor cytogenetic factor, $t(8;14)(q24;q32)$, was 60 years. Uncommon translocations, such

as t(4;11)(q21;q23) and t(1;19)(q23;p13), occurred less frequently. Low hypodiploidy/near triploidy, another adverse cytogenetic feature, was also associated with older age. Likewise, most of the patients with a complex karyotype (≥ 5 chromosomal abnormalities) were older than 60 years. Because of the greater frequency of poor-risk cytogenetic features in elderly patients with ALL, the disease is inherently more difficult to treat.

Management of ALL in Older Patients

In elderly patients, changes in organ function and physiology can affect the pharmacology of ALL therapy. As a result, the risk for toxicity with the standard chemotherapies used in ALL is higher in older patients.⁷ Rubin and colleagues reported an increased risk for cytarabine neurotoxicity, which was independent of underlying kidney function, in older patients with leukemia.⁸ Anthracyclines cause heart failure more frequently in older patients than in young adults. Old age appears to be inherently associated with a greater sensitivity to anthracycline toxicity. However, the reason for the increased sensitivity is not known with certainty.^{9,10} Other frequent problems include neuropathy and constipation associated with vincristine, and hyperglycemia induced by corticosteroids.

Aging is associated with enhanced vulnerability to acute liver injury and an increased incidence of various liver diseases, including alcoholic liver disease, non-alcoholic fatty liver disease, and hepatitis C.¹¹ In older patients with ALL, asparaginase treatment is one of the leading causes of liver toxicity, and asparaginase-related liver toxicity is more likely to develop in patients older than 50 years.¹² The concurrent use of another potentially hepatotoxic agent may further increase the likelihood of liver damage. In one study, 30 patients (median age, 58 years) with ALL were treated with pediatric-inspired regimens containing asparaginase.¹³ Grade 3 or 4 hyperbilirubinemia developed in 8 patients (27%) and was most common in the patients concurrently receiving tyrosine kinase inhibitors (TKIs). Overall, the incidence of grade 3 or 4 liver toxicity with TKIs is not high. With certain TKIs, however, such as nilotinib (Tasigna, Novartis) and bosutinib (Bosulif, Pfizer), liver toxicity can be a dose-limiting factor.¹⁴ The combination of asparaginase and a TKI is more likely to induce liver toxicity and cause treatment interruptions or delays.

The mechanism of drug resistance also appears to be altered with aging. Leith and colleagues reported that the expression of multidrug resistance gene 1 encoding P-glycoprotein increases with age, occurring in 39% of older patients (>50 years) vs 17% of younger patients (<35 years) with leukemia.¹⁵ Older patients tend to have

lower response rates and higher adverse event rates, so that closer monitoring is warranted for these patients.

Polypharmacy is a common concern in older patients with cancer.¹⁶ A Canadian study evaluated 112 patients with newly diagnosed cancer who were 65 years of age or older; 92% were receiving a median of 5 prescription drugs before chemotherapy.¹⁷ More than one-third of the patients were taking medications with significant drug-drug interactions, and most were receiving medications that either induced or inhibited cytochrome P-450, such as antidepressants, antifungals, antibiotics, and herbal supplements, including St John's wort. Each patient's prescription and over-the-counter medications should be carefully reviewed for potential interaction with antineoplastic agents. Any unnecessary or nonessential medication should be discontinued accordingly to minimize complications.

New Treatment Options for Older Patients With ALL

Older patients have been underrepresented in frontline clinical trials of ALL. With few exceptions, enrollment in studies has been limited owing to age cutoffs (60 or 65 years) or underlying comorbidities. As a result, we do not have well-established guidelines to make treatment decisions for older patients. The literature shows that the outcomes in elderly patients who have ALL treated with conventional intensive chemotherapy regimens are profoundly worse than those of younger adults (Table 1). The complete response (CR) rate range between 41% and 80% for patients older than 50 or 60 years. Accordingly, the 5-year overall survival (OS) rate varies between 17% and 23%. In a Cancer and Leukemia Group B (CALGB) study in which 759 adult patients with newly diagnosed ALL were treated between 1988 and 2002, the CR rate and 3-year OS rate were 57% and 12%, respectively, for those 60 years and older.¹⁸ For younger patients (30-59 years), the CR rate and 3-year OS were remarkably better, at 81% and 38%, respectively.

At our institution, the administration of intensive chemotherapy (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone [hyper-CVAD]) in older (≥ 60 years) patients with ALL generated a CR rate similar to that seen in younger (<60 years) patients: 84% vs 92%, respectively.¹⁹ However, 34% of the older patients died while in CR, mainly owing to infections. Not surprisingly, their 5-year OS rate was also poor, at approximately 20%. In contrast, the death rate of younger patients in CR and their 5-year OS rate were 7% and 48%, respectively. Historically, depending on the intensity of the chemotherapy, treatment-related mortality ranged from 16% to 37%.

Table 1. Prospective Studies in Older Patients With Acute Lymphoblastic Leukemia

Clinical Study	Year ^a	Age, y	N	CR Rate, %	Induction Death Rate, %	Overall Survival Rate, %
SWOG 8419 ⁴⁶	1985	>50	85	41	37	9 at 3 y
CALGB ¹⁸	1988	≥60	129	57	NR	12 at 3 y
GIMEMA ALL-0208 ⁴⁷	1988	50-60	121	68	NR	15 at 8 y
MD Anderson ⁴⁸	1992	≥60	44	80	16	17 at 5 y
MRC UKALL XII/ ECOG 2993 ⁴⁹	1993	55-65	100	73	18	21 at 5 y
SWOG 9400 ⁵⁰	1995	50-65	43	63	NR	23 at 5 y
PETHEMA ALL-96 ⁵¹	1996	≥55	33	58	36	39 at 2 y

CALGB, Cancer and Leukemia Group B; CR, complete response; ECOG, Eastern Cooperative Oncology Group; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; MRC UKALL, Medical Research Council Working Party on Leukaemia in Children UK National Acute Lymphoblastic Leukaemia Trial; N, number of patients enrolled; NR, not reported; PETHEMA, Programa Español de Tratamientos en Hematología; SWOG, Southwest Oncology Group; y, years.

^aStart year of study.

The most significant challenge in treating older patients with ALL is minimizing the risk for early death while simultaneously avoiding unnecessary attenuation of the treatment intensity. Significant advances have been made in the past decade toward understanding ALL biology and developing novel therapeutic agents. Targeted therapies aimed at CD19 and CD22 cell surface antigens and the BCR-ABL1 oncoprotein are major breakthroughs that may allow the development of less intensive but more effective treatment regimens.

Treatments for Philadelphia Chromosome-Negative ALL

Blinatumomab

The presence of CD19 expression in more than 95% of B-cell ALL blasts makes it an attractive target for treatment.²⁰ Blinatumomab (Blinicyto, Amgen) is a bispecific T-cell engager (BiTE) monoclonal antibody that directs cytotoxic T cells to CD19-expressing malignant B cells.²¹ It brings CD3-positive T cells into proximity with CD19-positive B cells, which results in the T-cell-mediated lysis of malignant B cells.²² In a confirmatory study, 189 patients aged 18 to 79 years with relapsed or refractory Ph-negative B-cell ALL received single-agent blinatumomab.²³ Of these, 81 (43%) had a CR or a CR with partial hematologic recovery (CRh), and 82% of the responders tested negative for minimal residual disease (MRD). A total of 32 (40%) responders underwent allogeneic stem cell transplant (SCT). With a median follow-up of 9.8 months, the median OS was 6.1 months.

The randomized TOWER study (Phase 3 Trial of Blinatumomab vs Investigator's Choice of Chemotherapy

in Patients With Relapsed or Refractory ALL) compared blinatumomab vs investigator's choice of chemotherapy in patients with relapsed or refractory ALL.²⁴ More than 400 patients with relapsed or refractory Ph-negative ALL were randomly assigned to either blinatumomab (n=271) or standard-of-care chemotherapy (n=134). The overall response rates were 45% and 30% ($P=.007$), respectively. The molecular remission rates among the responders, defined as those with fewer than 10^{-4} blasts in the first 12 weeks, were 75% and 48%, respectively. Blinatumomab prolonged the primary study endpoint of OS; the median OS was 7.7 months with blinatumomab and 4.0 months with standard-of-care chemotherapy ($P=.012$). The adverse effect profiles were similar for blinatumomab and standard of care. Blinatumomab also delayed the time to clinically meaningful deterioration in health-related quality of life (HRQoL).²⁵

The absence of upper age limits in the eligibility criteria of the phase 2 studies allowed an assessment of outcomes in the older patients treated with blinatumomab. In a recent study, the authors pooled the data from the previously mentioned studies^{23,26} and compared the efficacy and tolerability of blinatumomab in older patients (≥65 years) with its efficacy and tolerability in younger adults.²⁷ This study showed that the response rate and adverse event rate in older adults treated with blinatumomab were similar to those in younger adults, except for an increase in neurologic toxicity in the older patients. A total of 261 patients with relapsed/refractory B-cell ALL treated with blinatumomab were evaluated. Of these, 36 (14%) were 65 years of age or older and 225 (86%) were younger than 65 years. The CR-plus-CRh rate was 56% in the older patients and 46% in younger patients. The

rate of MRD negativity was 60% in the older responding patients and 70% in the younger responding patients. More younger than older responders proceeded to allogeneic SCT (59% vs 15%). Survival curves overlapped for the 2 age groups. OS was 5.5 months in the older patients and 7.6 months in the younger patients. Disease-free survival (DFS) was 7.4 months in both age groups. The incidence of grade 3 or higher adverse events in the older patients was similar to that in the younger patients (86% vs 80%), but the older patients had a higher rate of grade 3 or higher neurologic toxicity (28% vs 13%).

Studies assessing blinatumomab in the frontline setting are ongoing. The incorporation of blinatumomab into the frontline treatment of ALL may allow the implementation of less cytotoxic conventional chemotherapy. A phase 2 study has been investigating the hyperCVAD regimen in a sequential combination with blinatumomab as frontline therapy for adults with B-cell ALL. In this proposed study, patients will receive only 4 cycles of hyperCVAD (intensive phase) instead of the standard 8 cycles. As a substitute, patients will receive 4 cycles of blinatumomab after completing the intensive phase. This strategy may enable more patients to tolerate the prescribed regimen completely and improve outcomes. The omission of half of the intensive chemotherapy promises better tolerability in older patients with ALL.

Inotuzumab Ozogamicin

CD22 is a B-cell lineage antigen that is present on the surface of almost all B-ALL blasts. It is also an endocytic receptor to which an antibody-drug conjugate (ADC) can bind, permitting the drug to be carried into the cell without extracellular shedding.²⁸ Inotuzumab ozogamicin is an ADC in which a calicheamicin-derived cytotoxic moiety is attached to a humanized monoclonal anti-CD22 antibody. After it has been internalized by the leukemic blast, calicheamicin is released and exerts its cytotoxic activity by binding to the minor groove of DNA. Inotuzumab has been shown to be an effective regimen for the treatment of relapsed/refractory ALL. In a phase 2 clinical trial, single-agent inotuzumab was tested in 49 patients with heavily pretreated B-cell ALL; 73% of the patients were at salvage 2 or beyond.²⁹ Inotuzumab was administered as a single dose every 3 to 4 weeks. Of the 49 patients, 28 (57%) had a CR or CR with incomplete recovery of neutrophil and platelet counts (CRi). Of the responders, 63% achieved MRD negativity. The response rate in the patients 60 years of age or older was similar to that in the patients younger than 60 years: 58% vs 57%, respectively. The median OS was 5.1 months. Of the 49 patients, 22 (45%) proceeded to allogeneic SCT. In another phase 2 study, 41 patients with relapsed/refractory B-cell ALL were treated with a weekly dose of inotuzumab.³⁰ Of the

41 patients, 24 (59%) achieved a CR or CRi. Of the responders, 70% achieved MRD negativity. The median OS was 7.3 months.

Recently, a phase 3 study tested the efficacy and safety of inotuzumab in patients with relapsed/refractory B-cell ALL.³¹ A total of 326 patients underwent 1:1 randomization to receive inotuzumab or standard-of-care treatment with fludarabine/cytarabine, mitoxantrone/cytarabine, or a high-dose cytarabine-based regimen. The first 218 patients were included in the primary intent-to-treat analysis. Inotuzumab was administered for up to 6 cycles. The objective response rates were 88% (CR rate, 81%) with inotuzumab and 32% (CR rate, 29%) with standard-of-care chemotherapy ($P < .0001$). Among the responders, the MRD negativity rates were 78% and 28% ($P < .0001$), respectively. The median progression-free survival (PFS) was 5.0 months with inotuzumab and 1.8 months with standard-of-care chemotherapy ($P < .001$). The median OS was 7.7 months with inotuzumab vs 6.7 months with standard-of-care chemotherapy ($P = .02$; hazard ratio, 0.77). The 2-year OS rates were 23% and 10%, respectively. In a subgroup analysis of patients older than 55 years, the CR/CRi rates were 80% with inotuzumab and 25% with standard-of-care chemotherapy. Among the 109 patients treated with inotuzumab, the response rates and MRD negativity rates were similar for the patients aged 55 years and older ($n = 43$) and those younger than 55 years ($n = 66$): 80% vs 81% and 86% vs 74%, respectively. Age did not affect the median CR duration among the patients treated with inotuzumab, which was 5.2 months in the older and 5.4 months in the younger adults. Of those treated with inotuzumab, 23% ($n = 12$) of the older patients and 42% ($n = 36$) of the younger patients underwent allogeneic SCT. Inotuzumab-related neutropenia, thrombocytopenia, and anemia were more common in the older patients. Apart from hematologic toxicities, the types and rates of adverse events were similar in the older and younger adults.

Inotuzumab also has been tested in the frontline setting in older patients with Ph-negative B-cell ALL. In a phase 2 study, 47 patients with a median age of 68 years (range, 60-81) received low-dose hyperCVD in combination with inotuzumab.³² The overall response rate was 98% (CR, 84% and CR with incomplete platelet recovery, 12%), and all responding patients achieved MRD negativity within week 12 of therapy. The median PFS and OS have not been reached. The 3-year PFS and OS rates were 87% and 70%, respectively. Survival with low-dose hyperCVD plus inotuzumab was better than survival in historical data from similar patients ($n = 42$) treated with full-dose hyperCVAD; the 2-year OS rates were 64% and 38%, respectively. The most common grade 3 or higher adverse events were thrombocytopenia (79%), infections

Table 2. Prospective Studies in Older Patients With Ph-Positive Acute Lymphoblastic Leukemia

Study	Year*	Age, y	N	Induction → Consolidation	CR Rate, %	Overall Survival Rate, %
GIMEMA LAL0201-B ⁵²	2000	>60	30	IM + Prednisone → IM + PC	100	74 at 1 y
GMALL ⁵³	2002	>55	28	IM → IM + CH	96	57 at 1.5 y
GRAALL AFR09 ⁵⁴	2003	>55	30	CH → IM + CH	72	66 at 1 y
EWALL ³³	2007	>55	71	DAS + CH → DAS + CH	96	36 at 5 y

→, followed by; CH, chemotherapy; CR, complete response; DAS, dasatinib; EWALL, European ALL Working Group; GIMEMA, Gruppo Italiano Malattie Ematologiche dell'Adulto; GMALL, German Multicenter Study Group for Adult ALL; GRAALL, Group for Research on Adult Acute Lymphoblastic Leukemia; IM, imatinib; N, number of patients enrolled; PC, physician choice; Ph, Philadelphia chromosome; y, year(s).

*Start year of study.

during consolidation (74%), transaminitis (19%), and hyperbilirubinemia (17%). Overall, veno-occlusive disease developed in 4 patients, and 2 of them died of complications related to veno-occlusive disease. Encouraging response rates and a reasonable toxicity profile make the combination of inotuzumab and low-dose chemotherapy an attractive option for elderly patients with ALL, but longer follow-up and randomized studies are needed to confirm the findings.

Treatments for Philadelphia Chromosome-Positive ALL

The use of TKIs has improved the outcomes of older patients with Ph-positive ALL (Table 2). Studies combining dasatinib (Sprycel, Bristol-Myers Squibb) with low-intensity chemotherapy have shown encouraging results. In the EWALL-Ph-01 international study (European Working Group on Adult ALL Study Number 01 for Ph+ ALL), which studied patients at least 55 years of age with newly diagnosed Ph-positive ALL, this treatment approach yielded a CR rate of 96%. The estimated 3- and 5-year relapse-free survival rates were 33% and 28%, respectively, and the respective OS rates were 41% and 36%.³³ Among 36 patients who had ALL relapse, 24 had a T315I mutation. Similar results were recently reported by Chiaretti and colleagues from the Gruppo Italiano Malattie Ematologiche dell'Adulto (Multicenter Total Therapy GIMEMA LAL 1509 Protocol for De Novo Adult Ph+ Acute Lymphoblastic Leukemia Patients); in this study, dasatinib was combined with corticosteroids in 60 patients (median age, 42 years).³⁴ Near the end of 85 days, 97% of the patients were in complete hematologic remission (CHR), but only 19% had achieved a complete molecular response (CMR). The 3-year DFS and OS rates were 49% and 58%, respectively. In a multivariate

analysis, the achievement of CMR was an independent predictor of better survival.

Ponatinib (Iclusig, Ariad), a pan BCR-ABL inhibitor, has been shown to have significant activity against native and mutated TKIs, including those with T315I. In a recently reported trial, a combination of ponatinib and hyperCVAD was used as the frontline therapy in 53 patients with Ph-positive ALL whose median age was 54 years (range, 5-80 years).³⁵ All patients who received the treatment achieved CR. The overall MRD negativity rate was 98%. With a median follow-up of 33 months, 44 patients (83%) were alive and in CR. Of the 53 patients, 10 underwent SCT, and the landmark analysis showed no significant difference in 3-year CR rates (SCT, 88%; no SCT, 79%; $P=.48$) and 3-year OS rates (SCT, 79%; no SCT, 92%; $P=.31$). The 4-year OS rate in patients achieving MRD negativity by 3 months was superior to that of the patients who still had MRD positivity after the 3-month mark (66% vs 36%; $P=.0009$). Successful outcomes reported in this study suggest that with the use of highly efficacious TKIs such as ponatinib, the poor prognosis associated with Ph positivity in ALL may be eliminated. Furthermore, SCT may not be needed in first CR, especially in those with early MRD negativity. However, an increased incidence of cardiovascular adverse events appeared to be a concern in patients treated with full-dose (45 mg daily) ponatinib. There were 3 patients who died of myocardial infarction, and another 3 patients had serious thrombotic events; 2 of the events were deemed to be treatment-related. Recent data showed that lowering the ponatinib dose may decrease the cardiovascular event rate without decreasing efficacy.³⁶ Currently, lower-dose ponatinib with an adjusted schedule is being tested in the same trial.

For older patients with Ph-positive ALL, TKIs combined with less-intensive induction followed by optimized

consolidations appears to be a promising approach. Clinical trials investigating the bosutinib/inotuzumab combination and the blinatumomab/ponatinib combination are in progress.

Allogeneic Stem Cell Transplant in First Complete Response

Recent data highlight the significance of MRD in determining the need for SCT in patients with ALL. MRD status has shown promise in disease risk stratification. MRD positivity at any time is associated with a high risk for relapse and poor survival. However, there is no consensus on the role of MRD status in treatment decision making owing to the lack of a standardized definition of MRD positivity and timing of MRD testing in adult patients. Several reports have addressed the use of MRD level in clinical decision making for SCT. In one study, the Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) found the lack of an early MRD response to be a valuable tool for selecting patients who might benefit from SCT in first CR.³⁷ Overall, 522 patients who were deemed to have high-risk Ph-negative ALL were enrolled in the study while in first CR. All patients were eligible for SCT; 330 of them had an available donor, and 282 underwent transplant. The 5-year OS rates were similar, approximately 60%, whether SCT was performed or not. However, patients who had an MRD level of at least 10^{-3} after first induction benefited from SCT; the hazard ratios for PFS and OS were 0.40 (0.23-0.69) and 0.41 (0.23-0.74), respectively. In contrast, SCT provided no additional benefit when the MRD level was less than 10^{-3} ; the hazard ratios for PFS and OS were 1.37 (0.81-2.32) and 1.47 (0.85-2.54), respectively. Similarly, the Programa Español de Tratamientos en Hematología (PETHEMA) group reported that avoiding SCT was associated with superior PFS and OS in patients with ALL who achieved MRD negativity after intensive chemotherapy.³⁸ Altogether, these results suggest the ability of the MRD level to identify patients who might benefit from SCT, while also proving that SCT should be avoided in MRD-negative patients owing to the low risk for relapse. However, the data should be interpreted cautiously for elderly patients because both the GRAALL and PETHEMA studies excluded patients older than 60 years.

Older patients usually are not candidates for SCT because the transplant-related mortality rate is expected to be high. In the last decade, several studies reported promising results with the use of reduced-intensity conditioning in older adults. In a selected group of older patients with a median age of 45 to 56 years, reduced-intensity conditioning resulted in OS rates of

18% to 48%, transplant-related mortality rates of 21% to 28%, and relapse rates of 36% to 50%.³⁹⁻⁴⁴ In these studies, the proportion of patients receiving SCT in first CR varied between 9% and 83%, and patients had lower relapse rates when SCT was received in first CR.

Few studies have compared SCT and no-SCT approaches for patients in first CR. In a recent report, the authors analyzed the database of the Center for International Blood and Marrow Transplant Research (CIBMTR) and identified 422 patients aged 18 to 50 years with Ph-negative ALL who underwent SCT in first CR after receiving pediatric-inspired intensive chemotherapy.⁴⁵ An age-matched cohort of 108 patients with Ph-negative ALL who received only chemotherapy was compared with the patients who received SCT. MRD was not part of the analysis. However, the time to achieve CR was significantly longer in the SCT group than in the chemotherapy-alone group (≥ 8 weeks in 47% vs 1% of patients). At 4-year follow-up, the relapse rates were similar in the SCT and no-SCT groups: 24% and 23%, respectively. Nonrelapse mortality was 37% in the SCT recipients, compared with 6% in the patients who did not receive SCT ($P < .001$). The OS rate was worse in the SCT group than in the no-SCT group: 45% vs 73%, respectively ($P < .001$). In multivariate analysis, older age (30-50 years) was found to be independently associated with a high risk for transplant-related mortality. In a recent phase 2 trial, the role of SCT in first CR was evaluated in older patients with ALL (median age, 58 years; range, 51-72) who received pediatric-inspired multiagent chemotherapy.¹³ Of the 30 patients enrolled (40% with Ph-positive disease), 20 achieved CR and 12 underwent SCT in first CR (reduced-intensity conditioning was used for patients > 60 years old). There were 8 patients who did not receive SCT owing to recurrent disease, chemotherapy toxicity, or lack of a suitable stem cell donor. After adjustment for the time to SCT, the OS rates were similar in the SCT recipients and the chemotherapy-only recipients (2-year OS rates, 65% vs 53%; $P = .43$). Also, MRD status before SCT did not affect OS. Altogether, these data suggest that SCT is safe and feasible in older patients, but it may not improve survival.

Future Perspectives

The treatment of older patients with ALL is an absolute unmet medical need. The outcomes for older patients with ALL have not changed in decades. Within the last 5 years, several new agents have been introduced into clinical practice. Blinatumomab and inotuzumab ozogamicin are active in patients with relapsed or newly diagnosed ALL. Because ALL is an uncommon disease, clinicians should strongly consider treatment in a clinical trial for

their older patients. If a trial is not available on site, these patients should be referred to tertiary centers for possible enrollment in a study. Innovative clinical trial designs with less-intensive treatment regimens and broad entry criteria should be favored. Age itself should no longer be one of the exclusion criteria. However, a detailed documentation of underlying comorbidities, cognitive function, and performance status, in addition to a social assessment, should be standard in all clinical trials for older patients with ALL.

Disclosures

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