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Release date: May 10, 2019; Expiration date: May 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate updates to the NCCN Guidelines for Acute Lymphoblastic Leukemia into the management of older adult patients with acute lymphoblastic leukemia
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Acute Lymphoblastic Leukemia, with a focus on upfront therapy in older adults and MRD monitoring/testing in response to treatment for acute lymphoblastic leukemia

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

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Individuals Who Provided Content Development and/or Authorship Assistance:

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Bijal Shah, MD, Vice Chair, has disclosed that he receives grant/research support from Jazz Pharmaceuticals Inc. and Incyte Corporation; serves as a scientific advisor for Celgene Corporation and Novartis Pharmaceuticals Corporation; serves on the product/speakers bureau for Amgen Inc.; and receives consulting fees/honoraria from PharmacyClics, Inc.

Matthew Wieduwilt, MD, PhD, Panel Member, has disclosed that he receives grant/research support from Amgen Inc., Merck & Co., Inc., Leadiant Biosciences, Inc., and Servier; and he has equity interest/stock options in Reata Pharmaceuticals, Inc.

Aaron Logan, MD, PhD, Panel Member, has disclosed that he receives grant/research support from Kite Pharma, Inc., PharmacyClics, Inc., and Astellas Pharma US, Inc.; and receives consulting fees/honoraria from Amgen Inc., Agios Pharmaceuticals, and Incyte Corporation.

Daniel J. DeAngelo, MD, PhD, Panel Member, has disclosed that he receives consulting fees/honoraria from Amgen Inc., Blueprint Medicines, Celgene Corporation, Incyte Corporation, Jazz Pharmaceuticals Inc., Novartis Pharmaceuticals Corporation, Pfizer Inc., Shire, and Takeda Pharmaceutical Company Ltd.; and receives grant/research support from AbbVie Inc., GlycoMimetics, Inc., Novartis Pharmaceuticals Corporation, and Blueprint Medicines.

Eunice S. Wang, MD, Panel Member, has disclosed that she is a scientific advisor for AbbVie Inc., and Otsuka Pharmaceutical Co., Ltd; receives consulting fees/honoraria from Amgen Inc.; receives grant/research support from ImmunoGen, Inc.; and is on the product/speakers bureau of Incyte Corporation and Novartis Pharmaceuticals Corporation.

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Mark Litzow, MD, Panel Member, has disclosed that he receives grant/research support from Astellas Pharma US, Inc.; Actinium Pharmaceuticals, Inc.; Novartis Pharmaceuticals Corporation; AbbVie Inc.; Pluristem Therapeutics Inc.; and Tolero Pharmaceuticals, Inc. He receives consulting fees from sanofi-aventis U.S. LLC.

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This activity is supported by educational grants from AstraZeneca, Celgene Corporation, Clovis Oncology, Eisai, Genentech, Genomic Health, Inc., Novartis, Taiho Oncology, Inc., and TESARO. This activity is supported by an independent educational grant from AbbVie. This activity is supported by educational funding provided by Amgen. This activity is supported by an unrestricted educational grant from Gilead Sciences, Medical Affairs.

Acute Lymphoblastic Leukemia, Version 1.2019

Featured Updates to the NCCN Guidelines

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ABSTRACT

Survival outcomes for older adults with acute lymphoblastic leukemia (ALL) are poor and optimal management is challenging due to higher-risk leukemia genetics, comorbidities, and lower tolerance to intensive therapy. A critical understanding of these factors guides the selection of frontline therapies and subsequent treatment strategies. In addition, there have been recent developments in minimal/measurable residual disease (MRD) testing and blinatumomab use in the context of MRD-positive disease after therapy. These NCCN Guidelines Insights discuss recent updates to the NCCN Guidelines for ALL regarding upfront therapy in older adults and MRD monitoring/testing in response to ALL treatment.

J Natl Compr Canc Netw 2019;17(5):414–423
doi: 10.6004/jnccn.2019.0024

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PRINCIPLES OF SYSTEMIC THERAPY - Treatment of Older Adults with ALL

- Older adults (defined as those aged 65 years and older) benefit from therapy, in spite of higher treatment-related morbidity and mortality.
- Careful assessment of comorbid conditions, performance status, and ability to attend to activities of daily living (ADLs) and instrumental ADLs (IADLs) is important when deciding treatment intensity.
- Dose reduction of pegylated asparaginase (1000 IU/m²), anthracycline (50% dose), and/or other myelosuppressive agents may be warranted.
- The categorization of regimens as low, moderate or high intensity is based on two factors: 1) the presence or absence of myelosuppressive cytotoxic agents, and 2) the relative dose intensity of the included agents.
- All regimens should include CNS prophylaxis, antimicrobial prophylaxis, and growth factor support.
- For appropriate fit individuals achieving remission, consideration of autologous or reduced-intensity allogeneic SCT may be appropriate. See the NCCN Guidelines for Older Adult Oncology. Discussion of ALL in the elderly can be found on OAO-C page 2 of 7.

INDUCTION REGIMENS for Ph-negative ALL – Adults aged ≥65 y

- **Low intensity**
 - ▶ Vincristine + prednisone¹
 - ▶ Prednisone, vincristine, methotrexate, and 6-mercaptopurine (POMP)²
- **Moderate intensity**
 - ▶ GMALL: Idarubicin + dexamethasone + vincristine + cyclophosphamide + cytarabine ± rituximab³
 - ▶ PETHEMA-based regimen⁴
 - ◊ ALLOLD07 regimen: vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate, and L-asparaginase
 - ▶ GRAALL: doxorubicin + vincristine + dexamethasone + cytarabine + cyclophosphamide⁵
 - ▶ Modified DFCI 91-01 protocol: dexamethasone, doxorubicin, vincristine, methotrexate, cytarabine, L-asparaginase, and IT chemotherapy⁶
- **High intensity**
 - ▶ Hyper-CVAD⁷ with dose-reduced cytarabine to 1 g/m²
 - ▶ CALGB 9111⁸ (cyclophosphamide, daunorubicin, vincristine, prednisone, and pegaspargase)

INDUCTION REGIMENS for Ph-positive ALL – Adults aged ≥65 y

- **Low intensity**
 - ▶ TKI (imatinib, dasatinib, nilotinib) ± corticosteroids⁹⁻¹²
 - ▶ TKI (dasatinib, imatinib) + vincristine + dexamethasone¹³⁻¹⁵
- **Moderate intensity**
 - ▶ EWALL: TKI (dasatinib, nilotinib) with multiagent chemotherapy (vincristine, dexamethasone, methotrexate, cytarabine, asparaginase)¹⁶
- **High intensity**^{17,18}
 - ▶ TKI (dasatinib, ponatinib) + HyperCVAD with dose-reduced cytarabine to 1 g/m²

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ALL-D
7 OF 8

Overview

An important factor in long-term survival of patients with acute lymphoblastic leukemia (ALL) is their response to front-line therapy. Relative to treatment outcomes in pediatric and young adult patients with ALL, prolonged survival rates for older adults, especially those aged >60 years, remain low at approximately 20%.¹⁻³ In Philadelphia chromosome (Ph)–positive ALL, however, the difference in overall survival (OS) and outcomes between older and younger patients is less than with Ph-negative ALL, due in part to the availability of well-tolerated, effective oral *BCR-ABL1* tyrosine kinase inhibitor (TKI) therapy.⁴⁻¹⁰

Current approaches to evaluating older adult patients with newly diagnosed ALL for treatment include assessment of leukemia genetics, fitness for therapy, and performance status. In particular, older adults are more likely to have ALL with high-risk genetics, including Ph-positive disease, *MLL* rearrangements, or *TP53* mutation.^{11,12} Notably, Ph-like B-ALL, a high-risk subgroup, is also common in older patients, estimated at 24% in one large series.¹³ Often superimposed on this high-risk genetic background is an increased incidence and severity of comorbid conditions, poor functional status, and lower systemic and hematopoietic reserve, culminating in higher rates

of adverse drug interactions and treatment-related death.¹¹ However, these findings should not be interpreted as an indication to withhold intensive therapy, but rather stress the importance of tailoring therapy, as highlighted by the German Multicenter Study Group for Adult ALL (GMALL).³ Unfortunately, older patients with newly diagnosed ALL often do not receive chemotherapy or bone marrow transplant, highlighting the need for guidance in this population.¹⁴⁻¹⁷

Minimal/Measurable residual disease (MRD) after therapy in ALL refers to the presence of leukemic cells below the threshold of detection using conventional morphologic methods, and is a strong predictive factor of outcomes in ALL across all age groups.¹⁸⁻²⁰ Advances in technology have improved the sensitivity of methods used for MRD assessment, including multiparametric flow cytometry, real-time quantitative PCR, and next-generation sequencing (NGS).²¹ Given that some older adults with ALL have lower tolerability for intensive regimens, which may affect response to therapy and contribute to the presence of MRD following the initial phases of treatment, there is a need for agents with reduced toxicity that have potent antileukemic activity. Blinatumomab, a bispecific anti-CD3/CD19 monoclonal antibody, has demonstrated superior

MINIMAL/MEASURABLE RESIDUAL DISEASE ASSESSMENT

- The optimal sample for MRD assessment is the first pull or early pull of the bone marrow aspirate.
- MRD in ALL refers to the presence of leukemic cells below the threshold of detection by conventional morphologic methods. Patients who achieved a CR by morphologic assessment alone can potentially harbor a large number of leukemic cells in the bone marrow.
- MRD is an essential component of patient evaluation over the course of sequential therapy. If patient is not treated in an academic center, there are commercially available tests available that should be used for MRD assessment.
- Studies in both children and adults with ALL have demonstrated the strong correlation between MRD and risks for relapse, as well as the prognostic significance of MRD measurements during and after initial induction therapy.¹
- The most frequently employed methods for MRD assessment include at least 6-color flow cytometry assays^{2,3} specifically designed to detect abnormal MRD immunophenotypes, real-time quantitative polymerase chain reaction (RQ-PCR) assays to detect fusion genes (eg, *BCR-ABL1*), and next-generation sequencing (NGS)-based assays, to detect clonal rearrangements in immunoglobulin (Ig) heavy chain genes and/or T-cell receptor (TCR) genes.
- Current 6-color flow cytometry can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-4}$ ($<0.01\%$) bone marrow mononuclear cells (MNCs).^{2,3} PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<1 \times 10^{-6}$ ($<0.0001\%$) bone MNCs.^{4,5} The concordance rate for detecting MRD between these methods is generally high.
- ▶ Timing of MRD assessment:
 - ◊ Upon completion of initial induction.
 - ◊ Additional time points should be guided by the regimen used.
 - ◊ Serial monitoring frequency may be increased in patients with molecular relapse or persistent low-level disease burden.

¹Berry DA, Zhou S, Higley H, et al. Association of minimal residual disease with clinical outcome in pediatric and adult lymphoblastic leukemia. *JAMA Oncol* 2017;3:e170580.

²Gaipa G, Cazzaniga G, Valsecchi MG, et al. Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia. *Haematologica* 2012;97(10):1582-1593.

³Denys B, van der Sluijs-Gelling AJ, Homburg C, et al. Improved flow cytometric detection of minimal residual disease in childhood acute lymphoblastic leukemia. *Leukemia* 2013;27:635-641.

⁴Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. *Leukemia* 2010;24:521-535.

⁵Campana D. Minimal residual disease in acute lymphoblastic leukemia. *Hematology Am Soc Hematol Educ Program* 2010;2010:7-12.

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ALL-F

efficacy compared with chemotherapy in younger and older adult patients with relapsed/refractory (R/R) ALL,²²⁻²⁴ and single-arm studies support its role in treating persistent MRD after upfront therapy.²⁵⁻²⁷

The NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines) for ALL provide recommendations regarding standard treatment approaches based on current evidence. These NCCN Guidelines Insights highlight important updates and summarize upfront treatment strategies relating to older adult patients (generally defined as ≥ 60 years) with ALL and discuss the use of MRD testing. Although the age cutoff for older adults has been set at 65 years in the guidelines, it should be noted that chronological age alone is not always a reliable surrogate for determining an individual patient's fitness for intensive therapy. Patients should be evaluated on an individual basis to determine fitness based on factors such as performance status, comorbidities, and end-organ function.

Upfront Therapy According to Intensity in Older Adults

Traditionally, induction regimens for adult ALL have been based on a backbone of vincristine, a corticosteroid,

and an anthracycline. However, it is important to tailor treatment to a patient's fitness to minimize treatment-related toxicities and improve clinical outcomes. With this in mind, during the 2019 update, the NCCN panel recommended regimens for older adults with ALL according to intensity and included additional regimens (see ALL-D 7 of 8, opposite page). The categorization of regimens as low-, moderate-, or high-intensity is based on 2 factors: (1) the presence or absence of myelosuppressive cytotoxic agents, and (2) the relative dose intensity of the included agents.

Induction Regimens for Ph-Negative ALL

High-Intensity Regimens

The CALGB 8811 trial evaluated a 5-drug induction regimen (vincristine, daunorubicin, prednisone, L-asparaginase, and cyclophosphamide) as part of an intensive chemotherapy regimen for patients with previously untreated ALL (N=197; Ph-positive in 29%; age 16-80 years).²⁸ Patients aged ≥ 60 years received a dose-adjusted regimen with a prednisone pulse for only 7 days and a 33% reduction of daunorubicin and cyclophosphamide doses. Among 18 patients aged ≥ 60 years, the likelihood

of complete remission (CR) and 3-year survival was considerably lower when compared with younger patients, largely due to high induction-related mortality (50%), contributing to a median OS of 1 month in this population.²⁸ The CALGB 9111 study evaluated the impact of adding granulocyte colony-stimulating factor (G-CSF) on neutrophil recovery after intensive therapy with the CALGB 8811 regimen (N=198; age 16–83 years).²⁹ Overall, G-CSF use was associated with significantly shorter duration of severe neutropenia ($P<.001$) and thrombocytopenia ($P=.003$), and earlier hospital discharge ($P=.02$).²⁹ Among the 41 patients aged ≥ 60 years randomized to G-CSF (n=21) or placebo (n=20), G-CSF use was associated with lower induction mortality (10% vs 25%); however, this failed to meet statistical significance. The reduction observed with induction mortality was accompanied by a similarly nonsignificant increase in CR rate for those receiving G-CSF (81% vs 55%; $P=.1$). For the entire elderly group, median OS was improved to 12 months, but 3-year OS remained poor at 17%.²⁹

The hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) is another commonly used intensive regimen for adult patients with ALL. A phase II study from MD Anderson Cancer Center (MDACC) evaluated hyper-CVAD in adolescents and adults with previously untreated ALL (N=288; age 15–92 years; Ph-positive in 17%).³⁰ Median OS for all patients was 32 months, and the 5-year OS rate was 38%. Among 59 patients aged ≥ 60 years, induction mortality was 15% (vs 2% in those aged <60 years), culminating in a CR rate of 80%. Notably, this was not associated with an increase in 5-year OS (17%).³⁰ A subsequent retrospective review from the same institution suggested that this may have been related to higher rates of death during remission (34%) relative to younger patients (7%).³¹

Based on retrospective analyses of data from adults with B-ALL treated in clinical trials, CD20 positivity (defined as CD20 expression on $>20\%$ of blasts) correlated with adverse outcomes measured by a higher cumulative incidence of relapse, decreased CR duration, or decreased survival.^{32,33} A phase II study from MDACC evaluated modified hyper-CVAD (which included an anthracycline intensification during the second cycle) with or without rituximab in previously untreated patients with Ph-negative B-ALL (N=282; age 13–83 years).³⁴ Patients with CD20-positive B-ALL treated with hyper-CVAD and rituximab experienced improved outcomes relative to historical controls, with a 3-year CR duration and OS rates of 67% and 61%, respectively.³⁴ Notably, older patients (aged ≥ 60 years) with CD20-positive disease demonstrated higher rates of MRD negativity with the inclusion of rituximab; however, this did not translate into a survival benefit, again largely due to increased

mortality in CR. It is worth noting that this high rate of death in CR for older patients may relate to anthracycline intensification as opposed to inclusion of rituximab.³⁵

Moderate-Intensity Regimens

In an effort to decrease toxicity, the GRAALL-SA1 study compared the efficacy and toxicity of pegylated liposomal doxorubicin (Peg-Dox) to continuous-infusion doxorubicin (CI-Dox) in elderly patients (age ≥ 55 years) with ALL.³⁶ In this moderate-intensity regimen containing vincristine, dexamethasone, and cyclophosphamide, patients were randomized to receive either CI-Dox (n=31; 12 mg/m²/d) or Peg-Dox (n=29; 40 mg/m²).³⁶ Compared with the CI-Dox arm, Peg-Dox was significantly associated with reduced toxicity and fewer infections, but no survival benefit was seen: the induction mortality rate was 8% (7% for CI-Dox vs 10% for Peg-Dox), the frequency of refractory disease after induction was 10% (3% for CI-Dox vs 17% for Peg-Dox; $P=.10$), and the CR rate was 82% (90% for CI-Dox vs 72% for Peg-Dox; $P=.10$).³⁶ At 2 years, the estimated incidence of death during CR was 26.5% (37% for CI-Dox vs 19% for Peg-Dox), and the OS and event-free survival (EFS) rates were statistically similar at 35% and 24% in the CI-Dox and Peg-Dox arms, respectively.³⁶

In a prospective trial, GMALL evaluated the efficacy of moderate-intensity regimens in older adult patients with Ph-negative ALL (N=268; age 55–85 years).³⁷ A major finding from this study included the importance of ECOG performance status (PS) *before* onset of ALL (ECOGb PS) in predicting induction mortality. ECOGb PS ≥ 2 correlated with higher induction mortality rates compared with ECOGb PS 0 to 1 (53% vs 7%, respectively; $P<.0001$).³⁷ In addition, the study showed that consolidation with native *Escherichia coli* (*E. coli*) asparaginase and pegylated asparaginase was feasible and well tolerated, and was associated with improvements in CR rates and 2-year OS in this older patient subset.³⁷

ALLOLD07, a phase II prospective study in older patients with Ph-negative ALL conducted by the Spanish PETHEMA group (N=56; age 56–79 years),^{38,39} was based on a protocol from the European Working Group for Adult ALL (EWALL). Treatment comprised a 4-week induction with dexamethasone, vincristine, idarubicin, cyclophosphamide, and cytarabine, followed by consolidation with intermediate-dose methotrexate and native *E. coli* asparaginase. The CR rate was 74%, with an early death rate of 13%, and median disease-free survival (DFS) was 8 months, with a median OS of 12 months. This group studied other adapted regimens for Ph-positive ALL and mature B-ALL, but the outcomes were poorest in the Ph-negative ALL group.³⁹

A retrospective analysis examined the efficacy of a modified version of a Dana-Farber Cancer Institute

(DFCI) pediatric protocol, DFCI 91-01,^{40,41} in adult patients with newly diagnosed ALL (N=51; age 60–79 years).⁴² Induction consisted of dexamethasone (in place of prednisone), doxorubicin, cytarabine, and reduced doses of methotrexate, vincristine, and native asparaginase. For patients who achieved CR, median time to recurrence was 30 months (range, 1–94 months).⁴² In patients with Ph-negative disease (n=35), the CR rate was 71%, with induction mortality and primary refractory rates of 20% and 9%, respectively.⁴² The 5-year DFS rate among those achieving CR was 57.4% (95% CI, 32.8%–75.8%), whereas the overall estimated 5-year OS was 40.5% (95% CI, 20.0%–60.2%).⁴²

Low-Intensity Regimens

For older adult patients with ALL who may also have multiple comorbidities, the utility of traditional chemotherapy backbones based on vincristine, corticosteroids, and an anthracycline is limited largely due to treatment-related toxicities.¹⁷ Attempts to identify optimal therapy in this population have included adaptations of palliative regimens including vincristine and corticosteroids, and POMP (6-mercaptopurine, vincristine, methotrexate, and prednisone).^{43–46} Although these regimens are unlikely to generate cure, they can palliate the disease and extend survival, with clinical outcomes similar to those achieved with more intensive protocols. It is important to note that older adults with ALL and multiple comorbidities have not typically qualified for clinical trials. To improve clinical outcomes, trials designed specifically for this population are needed, and should include novel, personalized approaches based on immunophenotype and/or genetic mutation status.

Induction Regimens for Ph-Positive ALL

High-Intensity Regimens

Building on the success of the hyper-CVAD regimen, successive studies from the MDACC group incorporated TKIs into this backbone, beginning with the first-generation TKI imatinib and followed by the second- and third-generation TKIs dasatinib and ponatinib, respectively, to explore their efficacy in Ph-positive ALL. The initial trial with imatinib and hyper-CVAD in patients with previously untreated or minimally treated ALL (n=54; age 17–84 years) demonstrated a 3-year OS rate of 54%.⁹ In a study evaluating the efficacy of dasatinib combined with hyper-CVAD in patients with previously untreated Ph-positive ALL (N=35; age 21–79 years [11 patients aged ≥60 years]), the 2-year OS and EFS rates were 64% and 57%, respectively.⁴⁷ A phase II trial examined the efficacy and safety of ponatinib, a TKI with activity against the T315I mutation in *BCR-ABL1*, combined with hyper-CVAD in patients with Ph-positive ALL (N=37; age,

≥18 years [12 patients aged ≥60 years]).⁵ Of the 32 patients with Ph-positive metaphases at the start of therapy, an overall complete cytogenetic response was observed in all (100%).⁵ However, it is worth noting that only half of the patients aged ≥60 years were able to complete therapy with this regimen, and were switched to alternate TKIs. The 2-year OS and EFS rates were 80% and 81%, respectively.⁵

Moderate-Intensity Regimens

Several completed studies evaluating the efficacy of TKIs combined with multiagent chemotherapy in patients with previously untreated ALL have shown improved outcomes, particularly when treatment was followed by allogeneic hematopoietic stem cell transplantation (HCT).^{48–50} In a subgroup of patients with Ph-positive ALL (n=94; age 19–66 years) from the Northern Italy Leukemia Group protocol 09/00, outcomes were compared between patients who received chemotherapy with imatinib (n=59) or without imatinib (n=35), with or without subsequent transplant.⁴⁸ Patients who received imatinib had significantly higher 5-year OS (38% vs 23%; *P*=.009) and DFS rates (39% vs 25%; *P*=.044) compared with those who did not receive imatinib.⁴⁸ The 5-year OS rates by treatment type were 47% for allogeneic HCT (n=45), 67% for autologous HCT (n=9), 30% for imatinib without HCT (n=15), and 7% for no imatinib and no HCT (n=13). The corresponding treatment-related mortality rates were 17%, 0%, 36%, and 23%, respectively.⁴⁸ A multicenter phase II study by Kim et al⁵¹ evaluated the impact of multiagent chemotherapy combined with nilotinib followed by transplant in patients with newly diagnosed Ph-positive ALL (n=90; age 17–71 years). Nilotinib was combined with chemotherapy during induction, consolidation, and maintenance phases. Of 90 evaluable patients, 82 (91%) experienced complete hematologic remission, and the 2-year hematologic relapse-free survival (RFS) and OS rates were both 72%.⁵¹

The EWALL-PH-02 study also evaluated the efficacy and safety of nilotinib with multiagent chemotherapy in older patients with Ph-positive ALL (n=79 [72 evaluable]; age 55–85 years).⁷ The CR rate was 94.4% and MRD response (*BCR-ABL1/ABL1* ratio ≤0.1%) increased from 41% after induction to 86% after consolidation 2. At 4 years, the EFS and OS rates were 42% and 47%, respectively. Using landmark analyses with median time to transplant as a cutoff, the 4-year OS rate was 61% in patients who underwent allogeneic HCT.

Low-Intensity Regimens

Excellent treatment outcomes have been observed using low-intensity regimens in patients with Ph-positive ALL. In the multicenter EWALL-PH-01 study, induction therapy with dasatinib combined with vincristine and

dexamethasone was evaluated in older patients with Ph-positive ALL (n=71; age 58–83 years). The CR rate after induction was 96% and MRD response (*BCR-ABL1/ABL1* ratio $\leq 0.1\%$) occurred in 65% of patients.⁸ At 3 years, RFS, EFS, and OS were 33% (95% CI, 22%–44%), 31% (95% CI, 21%–42%), and 41% (95% CI, 29%–52%), respectively.⁸ At 5 years, the cumulative incidence of relapse was 54% (95% CI, 42%–66%). These studies suggest that the use of TKIs, either alone or in combination with less intensive therapies (eg, corticosteroids $\pm$ vincristine), may provide an alternative treatment option for older patients with Ph-positive ALL for whom intensive regimens are not appropriate.

The provocative randomized GRAAPH 2005 trial examined the impact of treatment intensity during the induction phase in younger adult patients with ALL (n=268; age <60 years) using high-dose imatinib combined with vincristine and dexamethasone (arm A) or hyper-CVAD (arm B).⁵² Surprisingly, a reduction in treatment intensity during the induction phase resulted in improved overall response rates largely due to reductions in treatment-related toxicities.⁵² The impact of these data may extend to patients aged >60 years and these findings are likely to inform further studies in this population, although optimization of therapy beyond induction is under clinical investigation.

Some other low-intensity approaches include TKIs $\pm$ corticosteroids. In a study that randomly assigned older patients with Ph-positive ALL (N=55; age 54–79 years) to induction therapy with imatinib versus chemotherapy alone, followed by imatinib-containing consolidation therapy, the estimated 2-year OS rate was 42%; no significant difference was observed between induction treatment arms.⁵³ Median OS was numerically higher (but not statistically significant) among patients who received imatinib induction compared with those randomized to chemotherapy induction (23.5 vs 12.3 months). However, the incidence of severe adverse events was significantly lower with imatinib induction (39% vs 90%; $P=.005$), suggesting that induction therapy with imatinib may be better tolerated than chemotherapy in older patients with Ph-positive ALL.⁵³

A phase II study by GIMEMA (LAL0201-B) evaluated imatinib combined with corticosteroids in older patients with Ph-positive ALL (n=29 evaluable; age 61–83 years).⁵⁴ Patients received imatinib in combination with prednisone for induction. The estimated 1-year DFS and OS rates were 48% and 74%, respectively, and median OS was 20 months.⁵⁴ In a separate study from GIMEMA (LAL1205), patients with Ph-positive ALL (n=53 evaluable; age 23.8–76.5 years) received induction therapy with dasatinib and prednisone.⁴ Postinduction therapy included no further therapy (n=2), TKI only (n=19), TKI combined with chemotherapy (n=10) $\pm$ autologous HCT

(n=4), or allogeneic HCT (n=18). All patients experienced a CR after induction therapy. Median OS was 31 months and median DFS (calculated from day +85) was 21.5 months. At 20 months, the OS and DFS rates were 69% and 51%, respectively.⁴

MRD Management

The most frequently used methods for MRD quantification include multiparameter flow cytometry (eg, 6-color or higher) to detect leukemia-associated immunophenotypes, PCR assays to detect fusion genes (eg, *BCR-ABL1*), and NGS-based assays to detect clonal rearrangements in immunoglobulin and/or T-cell receptor genes (see ALL-F, page 417).^{55–62} Assays to detect alternative leukemia-specific fusion genes specifically using NGS (as opposed to PCR) are also in development, but are not recommended for MRD quantification outside the context of a clinical trial. The NCCN panel acknowledged the recent FDA approval of an NGS-based MRD test based on quantification of immunoreceptor genes in patients with ALL, but panel members agreed that both multiparameter flow cytometry or this FDA-approved NGS approach are suitable methods for MRD quantification.

Current multiparameter flow cytometry methods can detect leukemic cells at a sensitivity threshold of $<10^{-4}$ ($<0.01\%$) bone marrow mononuclear cells (MNCs), and PCR/NGS methods can detect leukemic cells at a sensitivity threshold of $<10^{-6}$ ($<0.0001\%$) bone marrow MNCs.^{56,58,61,62} The concordance rate for quantifying MRD between these methods is generally high at disease burdens 10^{-4} ($>0.01\%$), but NGS is able to detect MRD at lower thresholds.^{57,59,62–66} After discussing available data, the NCCN panel revised the text to reflect the sensitivity levels of both methods (see ALL-F, page 417). The combined or tandem use of both methods would allow for MRD monitoring in all patients, thereby avoiding potential false-negative results.^{58,64,67} However, this practice could lead to an increase in cost without a clear directive in terms of modification of treatment. Complementary to this point, the panel added language to indicate that the frequency of serial monitoring of MRD could be increased in patients with molecular relapse or persistent low-level disease burden (see ALL-F, page 417).⁶⁸

MRD Persistence and Blinatumomab

Blinatumomab first showed promising clinical efficacy as a means of eradicating persistent MRD after up-front chemotherapy. In a multicenter, single-arm phase II study, Topp et al²⁷ evaluated the efficacy of blinatumomab in patients with MRD-positive Ph-negative B-ALL (N=21; age 20–77 years). Patients were considered MRD-positive if they had never achieved MRD negativity before blinatumomab or had experienced a hematologic CR with MRD $\geq 10^{-4}$. After blinatumomab treatment,

16 of 20 evaluable patients were determined to be MRD-negative at a detection threshold of 10^{-4} .²⁷ After a median follow-up of 33 months, the hematologic RFS of the evaluable cohort was 61%.²⁶ Gökbüget et al²⁵ examined the efficacy of blinatumomab in an expanded cohort (N=116) using a higher threshold for MRD positivity (hematologic CR with MRD $\geq 10^{-3}$). After one 28-day cycle of blinatumomab, 88 of 113 evaluable patients achieved a complete MRD response, and the RFS rate at 18 months was 54%.²⁵ In both of these trials, most patients achieving MRD negativity after blinatumomab proceeded to allogeneic HCT, establishing blinatumomab as an effective “bridge to transplant” in MRD-positive patients. Subsequent studies of blinatumomab evaluated its ability to induce CR (including rapid MRD-negative responses) in patients with R/R B-precursor ALL.^{24,69,70} In March 2018, the FDA approved blinatumomab for the treatment of adult and pediatric patients with B-cell precursor ALL in first or second CR with MRD defined as disease $\geq 0.1\%$.

Consolidation therapy in ALL typically uses multi-agent chemotherapy with consideration of allogeneic HCT when feasible. Emerging data suggest that blinatumomab therapy can potentially minimize the exposure of older patients with ALL to intensive chemotherapy and treatment related–toxicities. In a study evaluating the efficacy of blinatumomab in adults with R/R ALL (n=36), hematologic response rates and incidence of grade ≥ 3 adverse events were similar between younger (<65 years) and older (≥ 65 years) adults, although the incidence of reversible grade ≥ 3 neurologic events was higher in older adults.²² In older adults, high transplant-related mortality rates may preclude the use of this modality,⁷¹ and there is a need for decreased-intensity chemotherapy approaches that maintain antileukemic activity while decreasing treatment-related morbidity.¹¹ Blinatumomab may be well-suited to achieving this goal and is a subject of ongoing clinical trials.

NCCN Recommendations

For fit older adult patients with ALL, the NCCN panel recommends treatment in a clinical trial, when possible. Other initial treatment approaches depend on the patient’s age, PS, and presence of comorbid conditions. For patients with Ph-negative ALL, treatment options include multiagent chemotherapy or palliative corticosteroids. Patients experiencing a CR after induction should be monitored for persistent MRD to identify potential candidates for blinatumomab. If the MRD status is negative or unavailable, consolidation with chemotherapy and maintenance therapy is recommended. For patients with Ph-positive ALL, treatment options include a TKI with corticosteroids and/or chemotherapy. In patients experiencing a CR after induction, MRD assessment should be performed before consolidation therapy with a TKI alone

or combined with corticosteroids and/or chemotherapy. In Ph-positive ALL, postconsolidation maintenance TKI therapy is recommended. It is generally recommended that initial MRD assessment be performed on completion of induction; however, the timing of additional time points for MRD evaluation should be guided by the treatment protocol used.⁷² In all cases, dose modifications may be required for chemotherapy agents as needed.

Treatment regimens should include adequate central nervous system prophylaxis for all patients, and a given treatment protocol should be followed in its entirety, from induction therapy to consolidation/delayed intensification to maintenance therapy. Consolidation with allogeneic reduced-intensity HCT may be considered if the patient is MRD-positive or has high-risk cytogenetic features. Other transplant considerations include PS, donor availability, and transplant center expertise in treating older patients. The optimal timing of HCT is unclear, although early transplant is preferred to avoid cumulative toxicities of the treatment regimen and to lessen risk of relapse before transplant. For fit patients, additional therapy should be considered to eliminate MRD before transplant. Blinatumomab may be particularly effective and well-tolerated in this setting. When patients experience less than a CR after induction, they should be managed as R/R disease.

Conclusions

Prognosis remains poor among older adults with B-ALL, and management is challenging in this patient population. Advances in therapeutic approaches, including more refined diagnostic approaches to genetic analyses, MRD assessments, and tailored therapeutic regimens, have contributed to improvements in survival. Use of lower and moderately intensive regimens and blinatumomab (in B-ALL) may allow older patients to receive therapy for longer durations, with the potential for prolonged OS with fewer toxicities. Independent of therapeutic approach, MRD quantification has emerged as a strong prognostic marker for relapse, and importantly, may be actionable with the use of blinatumomab and transplant. Several ongoing national trials are investigating strategies that incorporate targeted immunotherapies, including blinatumomab and inotuzumab ozogamicin, in upfront regimens for older patients with ALL. Emerging data suggest that Ph-like ALL is also prevalent in older adults,^{13,73} and therefore future studies are needed to determine the utility of TKIs and novel therapies in this setting.

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