NCCN Guidelines® Insights

Acute Lymphoblastic Leukemia, Version 1.2017

Featured Updates to the NCCN Guidelines

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Abstract

The prognosis for patients with newly diagnosed acute lymphoblastic leukemia (ALL) has improved with the use of more intensive chemotherapy regimens, tyrosine kinase inhibitors, targeted agents, and allogeneic hematopoietic cell transplantation. However, the management of relapsed or refractory (R/R) ALL remains challenging and prognosis is poor. The NCCN Guidelines for ALL provide recommendations on standard treatment approaches based on current evidence. These NCCN Guidelines Insights summarize treatment recommendations for R/R ALL and highlight important updates, and provide a summary of the panel's discussion and underlying data supporting the most recent recommendations for R/R ALL management.

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Learning Objectives:

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

- Integrate into professional practice the updates to the NCCN Guidelines for Acute Lymphoblastic Leukemia
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Acute Lymphoblastic Leukemia

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RELAPSED/REFRACTORY DISEASE

TREATMENT

^{dd}Isolated extramedullary relapse (both CNS and testicular) requires systemic therapy to prevent relapse in marrow.

^{ee}See NCCN Guidelines for Palliative Care.

^{ff}See Treatment Options Based on *BCR-ABL1* Mutation Profile (ALL-D 3 of 5).

^{gg}See Principles of Systemic Therapy (ALL-D 3 of 5).

^{hh}For patients with relapsed disease after allogeneic HCT, a second allogeneic HCT and/or donor lymphocyte infusion (DLI) can be considered.

ⁱⁱFor patients in late relapse (>3 years from initial diagnosis), consider treatment with the same induction regimen (See ALL-D 2 of 5).

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NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Acute lymphoblastic leukemia (ALL) is a heterogeneous hematologic disease characterized by the proliferation of immature lymphoid cells in the bone marrow, peripheral blood, and other organs.¹ The US age-adjusted incidence rate of ALL is 1.58 per 100,000 individuals per year,² with approximately 5,970 new cases and 1,440 deaths estimated in 2017.³ Risk factors for developing ALL include older age (>70 years), exposure to chemotherapy or radiation therapy, and genetic disorders, particularly Down syndrome.^{4,5} Although rare, other genetic conditions have been categorized as a risk factor for ALL and include neurofibromatosis,⁶ Klinefelter syndrome,⁷⁻⁹ Fanconi anemia,^{10,11} Shwachman-Diamond syndrome,^{12,13} Bloom syndrome,¹⁴ and ataxia telangiectasia.¹⁵

Cure rates and survival outcomes for patients with ALL have improved dramatically over the past several decades, primarily among children.¹⁶ Improvements are largely owed to advances in the

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PRINCIPLES OF SYSTEMIC THERAPY (3 of 5)

REGIMENS FOR RELAPSED OR REFRACTORY ALL^{a,g}**Ph-positive ALL:**

- Dasatinib^{27,28}
- Imatinib²⁹
- Ponatinib^{30,h}
- Nilotinib³¹
- Bosutinib³²
- Blinatumomab (after failure of 2 TKIs)³³
- The TKIs noted above may also be used in combination with any of the induction regimens noted on ALL-D 1 of 5 that were not previously given.
- **MOpAd regimen (category 2B):** methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease and TKI.³⁴
- The regimens listed below for Ph-negative ALL may be considered for Ph-positive ALL refractory to TKIs.

Ph-negative ALL:

- Blinatumomab (for B-ALL) (category 1)^{35,i}
- Cytarabine-containing regimens³⁶
- Alkylator combination regimens³⁷
- Nelarabine (for T-ALL)³⁸
- Augmented hyper-CVAD: hyper-fractionated cyclophosphamide, intensified vincristine, doxorubicin, intensified dexamethasone, and pegaspargase; alternating with high-dose methotrexate and cytarabine³⁹
- Vincristine sulfate liposome injection (VSLI)^{40,41}
- Clofarabine-containing regimens (for B-ALL)^{42,43}
- **MOpAd regimen:** methotrexate, vincristine, pegaspargase, dexamethasone; with rituximab for CD20-positive disease.³⁴

References (ALL-D 4 of 5)

Mutation	Treatment Recommendation
Y253H, E255K/V, or F359V/C/I	Dasatinib
F317L/V/I/C, T315A, or V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, or Y253H	Bosutinib
T315I	Ponatinib

^aAll regimens include CNS prophylaxis with systemic therapy (eg, methotrexate, cytarabine, 6-mercaptopurine) and/or IT therapy (eg, IT methotrexate, IT cytarabine; triple IT therapy with methotrexate, cytarabine, corticosteroid).

^gThe safety of relapsed/refractory regimens in older adults (≥65) has not been established. Please see ALL-E 5 of 5 for additional information.

^hPonatinib has activity against T315I mutations and is effective in treating patients with resistant or progressive disease on multiple TKIs. However, it is associated with a high frequency of serious vascular events (eg, strokes, heart attacks, tissue ischemia). The FDA indications are for the treatment of adult patients with T315I-positive Philadelphia chromosome-positive acute lymphoblastic leukemia (Ph+ ALL) and for the treatment of adult patients with Ph+ ALL for whom no other TKI therapy is indicated. For details, see http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203469s007s008lbl.pdf.

ⁱBlinatumomab may cause severe, life-threatening, or fatal adverse events, including cytokine release syndrome and neurologic toxicities. Understanding of the risk evaluation and mitigation strategy (REMS) program and/or experience in the use of the drug as well as resources to monitor the patient closely are essential. It is important that the instruction for blinatumomab product preparation (including admixing) and administration are strictly followed to minimize medication errors, including underdose and overdose. For details, see <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=SearchDrugDetails>.

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ALL-D
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understanding of the molecular genetics and pathogenesis of ALL, the incorporation of risk-adapted therapy, the advent of new targeted agents, and the use of allogeneic hematopoietic cell transplantation (HCT). However, the treatment of patients who experience relapse after initial therapy remains a challenge. Several large studies using conventional chemotherapy for relapsed adult patients have reported a median overall survival (OS) of 4.5 to 6.0 months and a 5-year OS rate of 3% to 10%.^{17–20} These poor outcomes have inspired clinical trials with novel tyrosine kinase inhibitors (TKIs; for Philadelphia chromosome [Ph]–positive ALL), targeted agents, and immunotherapies, fundamentally changing the treatment landscape for those with relapsed/refractory (R/R) ALL.^{21,22}

The NCCN Clinical Practical Guidelines in Oncology (NCCN Guidelines) for ALL provide recommendations on standard treatment approaches based on current evidence. The NCCN Panel updates the guidelines annually, with additional interim updates

as needed. These NCCN Guidelines Insights highlight important updates and summarize treatment recommendations for R/R ALL, along with the panel discussion of relevant supporting data.

Updates to the Treatment of R/R Ph-Positive ALL

Tyrosine Kinase Inhibitors

The emergence of resistance poses a challenge for patients relapsing after initial treatment with TKI-containing regimens. Point mutations within the *ABL* kinase domain and alternative signaling pathways mediated by the SRC family kinase have been implicated as mechanisms of resistance.^{23–25} The former has been identified in a large proportion of patients who experience disease recurrence after imatinib-containing therapy.^{26,27} Moreover, *ABL* kinase domain mutations may be present in a small group of imatinib-naïve patients even before initiation of any TKI therapy.^{28,29}

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Dasatinib and nilotinib are second-generation TKIs that have shown greater potency in inhibiting *BCR-ABL* compared with imatinib and in the retention of antileukemic activity in cells with certain imatinib-resistant *ABL* mutations.^{30–33} Both TKIs have been evaluated as single-agent therapy in patients with Ph-positive ALL resistant to imatinib.^{34–36} Dasatinib in combination with the hyper-CVAD regimen (hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone) was investigated in a phase II trial that included patients with Ph-positive relapsed ALL (n=19) and lymphoid blast phase (BP) chronic myelogenous leukemia (CML) (n=15).³⁷ An overall response rate (ORR) of 91% was obtained with 26 patients (84%) achieving complete cytogenetic remission, 13 (42%) experiencing complete molecular response, and 11 (35%) experiencing a major molecular response; 9 patients went on to receive allogeneic HCT, including 2 with ALL. In those with relapsed ALL, 30% remained in complete remission (CR) at 3 years with a 3-year OS of 26%. At the median follow-up of 52 months (range, 45–59 months), 2 patients (11%) with ALL were still alive.

Bosutinib, a second-generation TKI that acts as a dual inhibitor of *BCR-ABL* and SRC family kinases,^{38,39} was FDA-approved in September 2012 for the treatment of chronic phase, accelerated phase (AP), or BP Ph-positive CML in adult patients with resistance to prior TKI treatment based on an open-label, multicenter, phase I/II trial.³⁹ Efficacy and safety analyses of bosutinib monotherapy included patients with advanced leukemia (AP CML: n=79, BP CML: n=64, or ALL: n=24) previously treated with at least one TKI.^{40,41} Of the 22 evaluable patients with ALL, 2 (9%) attained or maintained a confirmed overall hematologic response for 4 years.⁴⁰ Common overall treatment-related adverse events reported in patients with advanced leukemia included diarrhea (74%), nausea (48%), and vomiting (44%).^{40,41} During the 2017 guideline update, bosutinib was added as a treatment option for R/R Ph-positive ALL (see ALL-D 3 of 5; page 1094).

Ponatinib is a third-generation TKI that was initially FDA-approved in December 2012 for the treatment of adult patients with chronic phase, AP, or BP Ph-positive CML or Ph-positive ALL, with resistance to prior therapy,⁴² and was added to the guideline as a treatment option for R/R Ph-positive

ALL in 2013. Although temporarily removed from the market in November 2013, ponatinib distribution resumed in December 2013 after revision to both the prescribing information and the risk evaluation and mitigation strategies (REMS) program to address the risk for serious cardiovascular adverse events. This TKI has been shown to inhibit both native and mutant forms of *BCR-ABL* (including those resulting from T315I mutation) in preclinical studies.⁴³ In a multicenter, open-label, phase II study (PACE trial; n=449), ponatinib showed substantial activity in patients with Ph-positive leukemias resistant or intolerant to second-generation TKIs.⁴⁴ A major hematologic response was observed in 41% of the subgroup with Ph-positive ALL (n=32). In the subset of patients with Ph-positive ALL with an *ABL* T315I mutation (n=22), a major hematologic response was observed in 36%.⁴⁴ Common overall treatment-related adverse events in the PACE trial included thrombocytopenia (37%), rash (34%), and dry skin (32%). Additionally, arterial thrombotic events were observed and 7.1% of patients experienced cardiovascular events,⁴⁴ although dose reduction may impart a lower risk.

Not all imatinib-resistant *ABL* mutations are susceptible to the newer TKIs. For instance, dasatinib is not as active against cells harboring the *ABL* mutations T315I, V299L, and F317L.^{25,31,45,46} Thus, for patients with disease resistant to TKI therapy, it is important to identify potential *ABL* mutations that may underlie the observed resistance to treatment. A panel of experts from European LeukemiaNet (ELN) published recommendations for the analysis of *ABL* kinase domain mutations in patients with CML and treatment options according to the presence of different *ABL* mutations.⁴⁷ Based on these published recommendations and other studies, during the 2017 guideline update, the panel included a table with TKI treatment options for R/R Ph-positive ALL based on *BCR-ABL1* mutation status (see ALL-D 3 of 5; page 1094).

Hematopoietic Cell Transplant

Treatment options are extremely limited for patients with Ph-positive ALL who experience relapse after receiving consolidation with allogeneic HCT. Some investigators have reported on the feasibility of inducing a second molecular CR with dasatinib in those who have experienced an early relapse

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after first allogeneic HCT, which allowed for a second allogeneic HCT.^{48,49} Studies that include donor lymphocyte infusion (DLI) to induce further graft-versus-leukemia effect in patients who experience relapse after allogeneic HCT have reported little to no benefit, although it has been suggested that this is due to an excessively high leukemic burden.^{50,51} Published case reports have suggested that the use of DLI for residual disease or molecular relapse (as noted by levels of *BCR-ABL* fusion mRNA measured with PCR) after allogeneic HCT may eliminate residual leukemic clones and thereby prevent overt hematologic relapse.^{52–54} Moreover, case reports have described using newer TKIs, such as dasatinib and nilotinib, along with DLI to manage relapse after allogeneic HCT.^{55,56} Although these approaches are promising, only limited data are available. Evidence from prospective studies is needed to establish the role of DLI, with or without TKIs, in the treatment of relapsed disease.

Blinatumomab

In December 2014, blinatumomab received a breakthrough designation by the FDA for the treatment of R/R Ph-negative precursor B-cell ALL (see “Updates to the Treatment of R/R Ph-Negative ALL,” facing page, for a detailed discussion of blinatumomab). In July 2017, blinatumomab received full approval from the FDA for the treatment of R/R precursor B-cell ALL (Ph-negative and Ph-positive). A follow-up, open-label, single-arm, multicenter phase II study evaluated the efficacy and safety of blinatumomab in patients with R/R Ph-positive ALL whose disease had progressed after imatinib and at least one second- or third-generation TKI (n=45).⁵⁷ During the first 2 cycles of blinatumomab, 36% achieved CR or CR with partial hematologic recovery (CR/CRh), and 88% of CR/CRh responders achieved a complete minimal residual disease (MRD) response.⁵⁷ Notably, responses were independent of T315I mutation status. During the 2017 update, blinatumomab was added as an option for R/R Ph-positive ALL after TKI failure (see ALL-9 and ALL-D 3 of 5; pages 1093 and 1094, respectively).

MOpAD regimen

A single-arm trial evaluating the efficacy of the MOAD regimen (methotrexate, vincristine, L-asparaginase, and dexamethasone) in newly diagnosed

adults with ALL (n=55) demonstrated a CR rate of 76% with a median CR duration of >12 months.⁵⁸ A phase II trial incorporated a new PEGylated formulation of L-asparaginase due to improved tolerability,⁵⁹ and examined the safety and efficacy of the MOpAD regimen (methotrexate, vincristine, PEG-L-asparaginase, and dexamethasone) in adults with R/R ALL (n=37).⁶⁰ For patients with Ph-positive ALL, TKIs (ie, imatinib, dasatinib, or nilotinib) were added to the regimen; if patients had CD20-positive B-cell ALL, rituximab was added to the regimen. The CR and ORR rates were 28% and 39%, respectively, with a median duration of response of 4.3 months.⁶⁰ Patients with Ph-positive ALL had CR and ORR rates of 50% and 67%, respectively.⁶⁰ The panel discussed adding this regimen and it was included as a category 2B option for R/R Ph-positive ALL (ALL-D 3 of 5, page 1094). This regimen may be considered in patients who have received a maximal dose of anthracycline and have cardiac dysfunction and limited performance status.

NCCN Recommendations

Mutation testing for the *ABL1* kinase domain is recommended in patients with Ph-positive ALL that has relapsed after or is refractory to initial TKI-containing therapy. The panel has largely adopted the recommendations for treatment options based on *ABL* mutation status for CML, as published by the ELN.⁴⁷ If not administered during initial induction, TKIs (imatinib, dasatinib, nilotinib, bosutinib, or ponatinib) are recommended options for patients with R/R Ph-positive ALL. For second- and third-generation TKIs, relevant *BCR-ABL1* mutations should be considered as outlined in the table on ALL-D 3 of 5 (page 1094). Due to the high frequency of serious vascular events with ponatinib therapy, the FDA indication is restricted to the treatment of patients with the T315I mutation or in those with disease resistant to other TKI therapies.

For all patients with R/R Ph-positive ALL, participation in a clinical trial is preferred. In the absence of an appropriate trial, patients may be considered for second-line therapy with an alternative TKI (ie, different from the TKI used as part of induction therapy) alone, TKI combined with multiagent chemotherapy, or TKI combined with corticosteroids (especially for elderly patients who may not tolerate multiagent combination therapy). These options

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should be combined with allogeneic HCT if a donor is available. Blinatumomab is an option if the patient is refractory to at least 2 TKIs.⁵⁷ For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI. For patients with Ph-positive ALL that is refractory to TKIs, regimens for R/R Ph-negative ALL can be considered.

Updates to the Treatment of R/R Ph-Negative ALL

Blinatumomab

A component of the growing arsenal of immunotherapies for cancer treatment, blinatumomab is a bi-specific anti-CD3/CD19 monoclonal antibody that showed high CR rates (69%; including rapid MRD-negative responses) in patients with R/R B-precursor ALL (n=25).^{61,62} Blinatumomab was approved by the FDA based on data from a large phase II confirmatory study of 189 patients with R/R Ph-negative B-cell ALL that demonstrated a CR or CR without platelet recovery (CRp) in 43% of patients within the first 2 cycles of treatment.^{63,64} In a follow-up prospective, multicenter, randomized phase III trial, patients with R/R B-cell precursor ALL (n=405) were assigned to receive either blinatumomab (n=271) or standard chemotherapy (n=134).⁶⁵ OS was longer in the blinatumomab group, with median OS at 7.7 months, compared with the standard chemotherapy group, with median OS at 4.0 months (95% CI, 0.55–0.93; *P*=.01).⁶⁵ Remission rates within 12 weeks after treatment initiation were significantly higher in the blinatumomab group than in the standard chemotherapy group with respect to both CR with full hematologic recovery (CR, 34% vs 16%; *P*<.001) and CR with full, partial, or incomplete hematologic recovery (CRi; CR, CRh, or CRi, 44% vs 25%; *P*<.001).⁶⁵ Of note, prespecified subgroup analyses of patients with high bone marrow count ($\geq 50\%$) at relapse demonstrated lower blinatumomab-mediated median survival and remission rates.⁶⁵

There are significant and unique side effects to blinatumomab treatment compared with the current standard-of-care regimens. The most significant toxicities noted in clinical studies are central nervous system (CNS) events and cytokine release syndrome (CRS). Neurologic toxicities have been reported in 50% of patients (median onset, 7 days) and grade

≥ 3 neurologic toxicities, including encephalopathy, convulsions, and disorientation, have occurred in 15% of patients.⁶⁶ CRS typically occurs within the first 2 days following initiation of blinatumomab infusion,⁶⁶ and symptoms include pyrexia, headache, nausea, asthenia, hypotension, increased transaminases, and increased total bilirubin. The incidence of adverse events can be reduced with monitoring for early intervention at onset of symptoms. However, the serious nature of these events underscores the importance of receiving treatment in a specialized cancer center that has experience with blinatumomab. Based on data from the phase III study demonstrating the efficacy of blinatumomab in R/R B-cell precursor ALL,⁶⁵ the panel changed the category of evidence from 2A to 1 (ALL-9 and ALL-D 3 of 5; pages 1093 and 1094, respectively) for the 2017 update.

Nelarabine

Nelarabine is a nucleoside analogue currently approved for the treatment of patients with T-cell ALL with unresponsive or relapsed disease after at least 2 chemotherapy regimens.⁶⁷ A phase II study of nelarabine monotherapy in children and adolescents with R/R T-cell ALL or T-cell non-Hodgkin's lymphoma (n=121) showed a 55% response rate among the subgroup with T-cell ALL with first bone marrow relapse (n=34) and a 27% response rate in the subgroup with a second or greater bone marrow relapse (n=36).⁶⁸ Major toxicities included grade ≥ 3 neurologic (both peripheral and CNS) adverse events in 18% of patients. Nelarabine as single-agent therapy was also evaluated in adults with R/R T-cell ALL or T-cell lymphoblastic leukemia in a phase II study (n=39; median age, 34 years; range, 16–66 years; median 2 prior regimens; T-cell ALL, n=26).⁶⁹ The CR rate (including CRi) was 31%; an additional 10% of patients experienced a partial remission. The median disease-free survival and OS were both 20 weeks and the 1-year OS rate was 28%. Grade 3 or 4 myelosuppression was common, but only one case of grade 4 CNS toxicity (reversible) was observed.⁶⁹

Augmented Hyper-CVAD

A phase II study from the University of Texas MD Anderson Cancer Center evaluated an augmented hyper-CVAD regimen, which incorporated asparaginase, intensified vincristine, and intensified

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dexamethasone, as therapy in adults with R/R ALL (n=90; median age, 34 years; range, 14–70 years; median 1 prior regimen).⁷⁰ Among evaluable patients (n=88), the CR rate was 47%; an additional 13% experienced a CRp and 5% experienced a partial remission. The 30-day mortality rate was 9% and median remission duration was 5 months. Median OS for all evaluable patients was 6.3 months; median OS was 10.2 months for patients who experienced a CR. In this study, 32% of patients were able to proceed to HCT.⁷⁰

Vincristine Sulfate Liposomal Injection

Vincristine sulfate liposome injection (VSLI) is a novel nanoparticle formulation of vincristine encapsulated in sphingomyelin and cholesterol liposomes; the liposome encapsulation prolongs the exposure of active drug in the circulation and may allow for delivery of increased doses of vincristine without increasing toxicities.^{71,72} VSLI was evaluated in an open-label, multicenter, phase II study in adult patients with Ph-negative ALL (n=65; median age, 31 years; range, 19–83 years) in second or greater relapse, or with disease that progressed after ≥2 prior lines of therapy (RALLY study).⁷³ The CR (CR + CRi) rate with single-agent VSLI was 20%. Median duration of CR was 23 weeks (range, 5–66 weeks), and median OS for all patients was 20 weeks (range, 2–94 weeks); median OS for those achieving a CR was 7.7 months.⁷³ The incidence of early induction death (30-day mortality rate) was 12%.⁷³ These outcomes appeared favorable compared with published single-center historical data in patients with Ph-negative ALL treated with other agents at second relapse (n=56; CR rate, 4%; median OS, 7.5 weeks; early induction death, 30%).^{73,74} The most common grade ≥3 treatment-related toxicities with VSLI included neuropathy (23%), neutropenia (15%), and thrombocytopenia (6%).⁷³ Based on phase II data from the RALLY study, VSLI was given accelerated FDA approval in September 2012 for the treatment of adult patients with Ph-negative B-cell ALL in second or greater relapse.⁷⁵ Confirmation of benefit from phase III studies is pending.

Clofarabine

Clofarabine is a nucleoside analogue approved for the treatment of pediatric patients (aged 1–21 years) with ALL that is R/R after at least 2 prior regimens.⁷⁶

In a phase II study of single-agent clofarabine in heavily pretreated pediatric patients with R/R ALL (n=61; median age, 12 years; range, 1–20 years), the response rate (CR + CRp) was 20%.⁷⁷ Single-agent clofarabine in this setting was associated with severe liver toxicities (generally reversible) and frequent febrile episodes, including grade 3 or 4 infections and febrile neutropenia.⁷⁷ Phase II studies evaluating the combination of clofarabine with cyclophosphamide and etoposide in pediatric patients with R/R ALL have resulted in response rates ranging from 44% to 52%.^{78,79} This combination has been associated with prolonged and severe myelosuppression, febrile episodes, severe infections (including sepsis or septic shock), mucositis, and liver toxicities including fatal veno-occlusive disease (the latter occurring in the post-allogeneic HCT setting).⁷⁸

There are limited studies of clofarabine combination regimens in adults with R/R disease. In a study from GRAALL, adult patients with R/R ALL (n=55) were treated with clofarabine in combination with conventional chemotherapy (cyclophosphamide [ENDEVOL cohort; median age, 53 years; range, 18–78 years], or a more intensive regimen with dexamethasone, mitoxantrone, etoposide, and PEG-asparaginase [VANDEVOL cohort; median age, 34 years; range, 19–67 years]). Patients in the ENDEVOL cohort achieved a CR of 50% (9 of 18), and those in the VANDEVOL cohort yielded a CR rate of 41% (15 of 37); median OS was 6.5 months after a median follow-up of 6 months.⁸⁰ The most common grade 3 or 4 toxicities included infection (58%) and liver toxicities (24%), with an early death rate of 11%.⁸⁰ Because the use of clofarabine-containing regimens require close monitoring and intensive supportive care measures, patients should only be treated in centers with expertise in the management of ALL, preferably in the context of a clinical trial.

MOpAD Regimen

Based on data summarized earlier,^{58–60} the panel discussed adding the MOpAD regimen for R/R Ph-negative ALL, and it was included as a category 2A option during the 2017 update (ALL-D 3 of 5; page 1094).

Hematopoietic Cell Transplant

HCT is the only potentially curative modality for R/R ALL. Based on findings from evidence-based

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review of the published literature, the American Society for Blood and Marrow Transplantation guidelines recommend HCT over chemotherapy alone for adult patients with ALL experiencing a second CR.⁸¹ Several studies have shown that for adolescent and young adult patients in second CR, allogeneic HCT may improve outcomes, particularly for those who have early bone marrow relapse or other high-risk factors.^{82–84} Seemingly contradictory data was reported in the COG CCG-1952 study that showed prognosis after early bone marrow relapse in patients with standard-risk ALL (age 1 to <10 years; WBC count $<50 \times 10^9/L$) remained poor with no apparent advantage of HCT, regardless of timing (ie, early or late) of bone marrow relapse.⁸⁵ However, data were not available on the conditioning regimen used for HCT in this study for comparison with other trials. The UKALLXII/ECOG2993 trial (n=609; age range, 15–60 years) examined the efficacy of transplantation after relapse in a subgroup of patients with relapsed ALL who had not received prior transplant.⁸⁶ Patients treated with HCT demonstrated a superior OS at 5 years compared with those treated with chemotherapy alone.⁸⁶ The Center for International Blood and Marrow Transplant Research (CIBMTR) conducted an analysis of outcomes of patients with ALL (n=582; median age, 29 years; range, <1–60 years) who underwent transplant during relapse.⁸⁷ At 3 years, the OS rate was 16% (95% CI, 13%–20%).⁸⁷ Response to salvage therapy before HCT may also predict outcome. One retrospective study showed 3-year OS and event-free survival estimates of 69% and 62%, respectively, for patients in second or later MRD-negative remission at HCT, similar to the outcomes of those who underwent HCT in MRD-negative first remission at the same center.⁸⁸

NCCN Recommendations

For patients with R/R Ph-negative ALL, the approach to second-line treatment may depend on the duration of the initial response. For late relapses (ie, occurring ≥ 36 months from initial diagnosis), re-treatment with the same induction regimen is a reasonable option. For other patients, participation in a clinical trial is preferred when possible. In the absence of an appropriate trial, for patients with R/R Ph-negative precursor B-cell ALL, blinatumomab is recommended. Other possible options include subsequent chemotherapy alone, with regimens contain-

ing clofarabine, nelarabine (for T-cell ALL), VSLI, augmented hyper-CVAD, MOpAD regimen, or other cytarabine- or alkylator-containing regimens, or chemotherapy with allogeneic HCT if a donor is available. For patients with disease that relapses after an initial allogeneic HCT, other options may include a second allogeneic HCT and/or DLI.

Emerging Treatment Options

Inotuzumab Ozogamicin

Inotuzumab ozogamicin (InO) is a calicheamicin-based antibody-drug conjugate targeting CD22. Based on encouraging single-agent phase II data,⁸⁹ a randomized study was conducted comparing InO with standard intensive chemotherapy regimens in Ph-negative or Ph-positive ALL in first or second relapse, defined as $>5\%$ marrow blasts (n=326). Compared with standard therapy, InO produced a significantly higher CR/CRi rate (80.7% vs 29.4%; $P<.001$), and higher MRD-negative rates (78.4% vs 28.1%; $P<.001$).⁹⁰ Notably, responses were consistent across most subgroups, including those with high marrow burden and those with Ph-positive leukemia. The overall incidence of severe adverse events were similar across treatment arms, with a higher incidence of hepatic veno-occlusive disease observed in the InO group, related in part to dual alkylator-based transplant conditioning administered in remission. These data translated into a significant benefit in the median duration of remission (4.6 vs 3.1 months; $P=.03$), median progression-free survival (5.0 vs 1.8 months; $P<.001$), and mean OS (13.9 vs 9.9 months; $P=.005$).⁹⁰

Chimeric Antigen Receptor T Cells

The generation of chimeric antigen receptor (CAR) T cells to treat ALL represents a significant advance in the field.⁹¹ CAR T-cell therapy relies on the genetic manipulation of a patients' T cells to engender a response against a leukemic cell-surface antigen, most commonly CD19.⁹² In an initial phase I study of 16 adult patients with R/R B-cell ALL, CAR T-cell therapy elicited a promising overall complete response rate of 88%.⁹³ A separate pilot study using a different CAR-T cell product (CTL019) in patients with relapsed B-cell ALL (n=30; 25 patients with age range 5–22 years; 5 patients with age range 26–60 years) observed similar results with CR achieved

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in 27 of 30 patients (90%).⁹⁴ Together these data inspired the development of larger multicenter trials of CAR T-cell therapy.⁹⁵ Relevant in this context are recent interim data from the ELIANA trial of CTL019 in 62 children and young adults with R/R B-ALL, which confirmed a high CR (and CR with incomplete blood count recovery) rate of 83%, all of which were notably MRD-negative.⁹⁶ This high response rate was associated with a 6-month relapse-free survival rate of 75% and a 6-month OS rate of 89%. As with blinatumomab, T-cell activation was accompanied by severe CRS and neurologic toxicity, as well as higher infectious risks—although treatment-related mortality remained low at 6%. Given these data, CTL019 was recommended for accelerated approval by the FDA Oncologic Drug Advisory Committee in July 2017.

Summary

This report highlights the updates to systemic therapy recommendations for the management of R/R ALL in the 2017 version of the NCCN Guidelines for ALL. Several factors are considered in the selection of an appropriate treatment strategy for R/R ALL based on the patient's age, performance status, end-organ reserve, end-organ dysfunction, and eligibility for transplant. Currently, HCT is the only cure for R/R ALL, but many patients are not eligible for transplant based on age or disease progression. Future and emerging therapeutic considerations may include CAR T-cells, antibody-drug conjugates (eg, InO), and other immunomodulatory agents.^{90,91,93,97} When possible, consistent with NCCN philosophy, the panel strongly encourages patient/physician participation in clinical trials.

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Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at <http://education.nccn.org/node/81547>; and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-

choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet

Posttest Questions

1. In the recently updated NCCN Guidelines for ALL, which of the following TKIs is a new treatment option for patients with R/R Ph-positive ALL?
 - a. Nilotinib
 - b. Ponatinib
 - c. Bosutinib
2. In the NCCN Guidelines for ALL, which of the following may be considered as first-line treatment options for R/R Ph-

positive and Ph-negative ALL based on the NCCN Guidelines?

- a. Blinatumomab
- b. MOPAD regimen
- c. Nelarabine
- d. a and b
- e. b and c
- f. All of the above

3. True or False: There are several established clinical studies examining clofarabine combination regimens in adults with R/R Ph-negative ALL.