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GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: leukemia-3. Acute lymphoblastic leukemia/lymphoblastic lymphoma: ALL/LBL

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Overview

Acute lymphoblastic leukemia (ALL) and lymphoblastic lymphoma (LBL) are both neoplasms derived from lymphoid progenitor cells and are considered to be essentially the same disease. Patients with a high proportion of lymphoblasts in the bone marrow are considered to have ALL and patients with a predominant mass in the lymphoid tissues and little bone marrow involvement are considered to have LBL. The distinction between the two is not always clear, but ALL is typically diagnosed when the percentage of lymphoblasts in the bone marrow is 25% or higher.

In the 2017 WHO Classification, lymphoid malignancies were classified into B-cell malignancies and T-cell/natural killer (NK) cell malignancies and sub-classified by the approximate stage of differentiation of normal lymphoid cells they resemble [1]. Essentially, ALL/LBL is classified by whether it originates in precursor B cells (called B-cell ALL/LBL) or precursor T cells (called T-cell ALL/LBL), and B-cell ALL/LBL is further classified as "not otherwise specified" or "with recurrent genetic abnormalities." Other provisional entities have also been added to B-cell and T-cell ALL/LBL (Table 1) [1]. The L3 type of the FAB classification [2] is part of the Burkitt lymphoma category of mature B-cell neoplasms, and is not included in the ALL/LBL category [1].

Primary therapy for ALL mainly consists of combination chemotherapy with anti-leukemic (anticancer) drugs highly effective against lymphoid neoplasms. Induction therapy, post-remission therapy (consolidation and maintenance therapy), and central nervous system (CNS) prophylaxis are performed.

Age and white blood cell (WBC) count have conventionally been considered important prognostic factors, but hypodiploidy (< 44 chromosomes), t(4;11) (q21;q23) and other *KMT2A* rearrangements, *IgH* translocation, t(9;22) (q34;q11.2) (Philadelphia chromosome; Ph), *BCR::ABL1*, complex karyotype, *BCR::ABL1*-like (Ph-like), and *IKZF1* mutation are now considered unfavorable prognostic factors

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[3]. Ph-positive ALL was recognized as poor-risk before tyrosine kinase inhibitors (TKIs) became available, but the prognosis has now improved with TKI therapy. In addition, minimal/measurable residual disease (MRD) has recently been proposed as a better predictor of prognosis than conventional prognostic factors.

Table 1 The 2017 WHO Classification of ALL/LBL

B-lymphoblastic leukemia/lymphoma
• B-lymphoblastic leukemia/lymphoma, NOS
• B-lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
• B-lymphoblastic leukemia/lymphoma with t(9;22)(q34.1;q11.2); BCR-ABL1
• B-lymphoblastic leukemia/lymphoma with t(v;11q23.3); KMT2A rearranged
• B-lymphoblastic leukemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
• B-lymphoblastic leukemia/lymphoma with hyperdiploidy
• B-lymphoblastic leukemia/lymphoma with hypodiploidy
• B-lymphoblastic leukemia/lymphoma with t(5;14)(q31.1;q32.3); IL3-IGH
• B-lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); TCF3-PBX1
• Provisional entity: B-lymphoblastic leukemia/lymphoma, BCR-ABL1-like
• Provisional entity: B-lymphoblastic leukemia/lymphoma with iAMP21
T-lymphoblastic leukemia/lymphoma
• Provisional entity: Early T-cell precursor lymphoblastic leukemia
• Provisional entity: Natural killer (NK) cell lymphoblastic leukemia/lymphoma

(From Reference 1)

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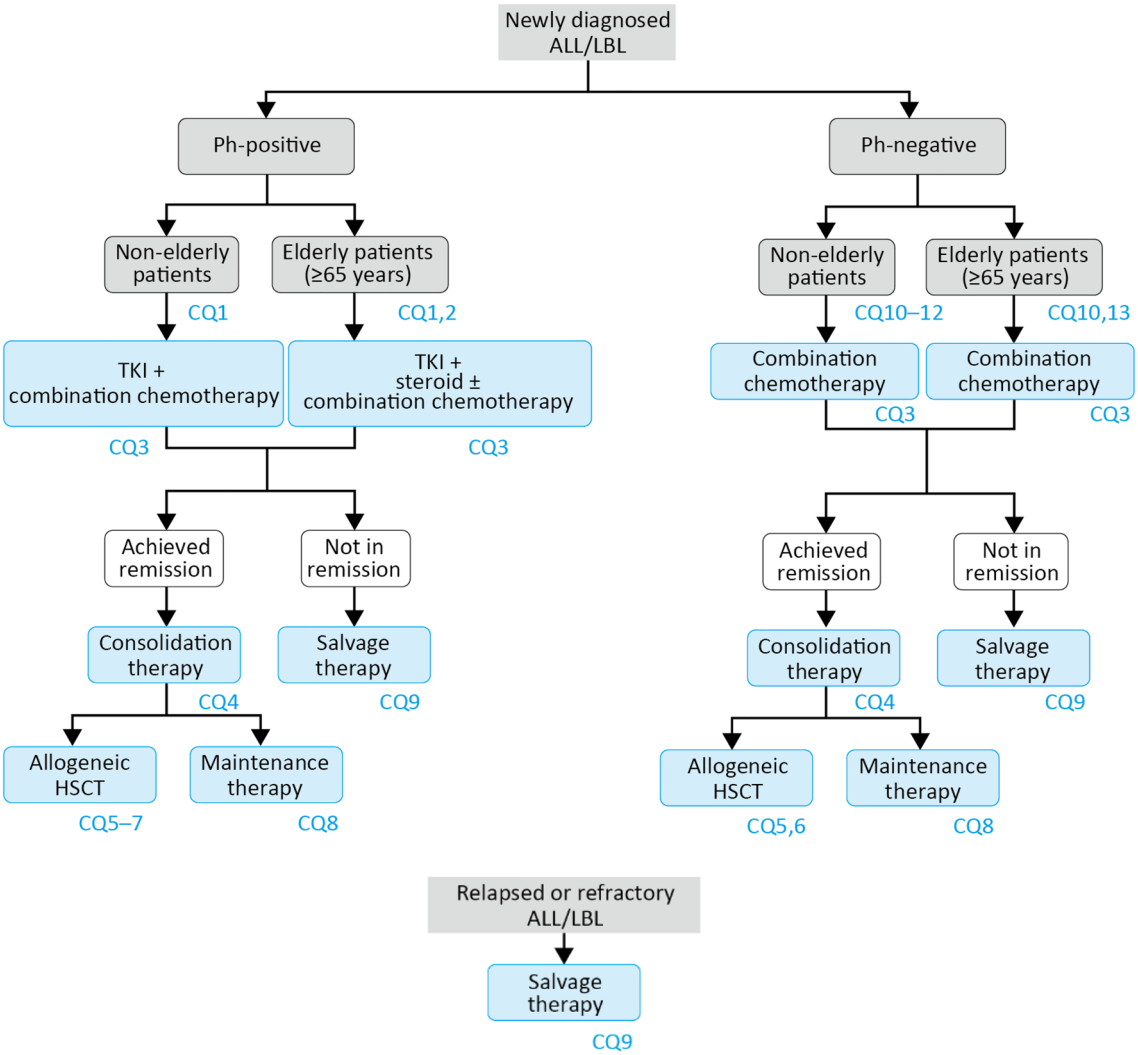
Algorithm



When selecting induction therapy, it is required to distinguish the patient as Ph-positive or negative. Chemotherapy regimens with a TKI are recommended for Ph-positive patients (CQ1, 2). Allogeneic hematopoietic stem cell transplantation (HSCT) is recommended for Ph-positive ALL in first remission (CQ5). Prophylactic TKI maintenance is not recommended while a patient is MRD-negative after allogeneic HSCT. However, preemptive TKI therapy is recommended once the patient becomes MRD-positive (CQ7). Induction with a TKI plus a steroid is recommended for elderly (≥ 65 years) patients with Ph-positive ALL. When possible, reduced-intensity consolidation and maintenance chemotherapy is recommended in addition to TKI therapy (CQ2). However, continuation of TKI maintenance therapy for at least 5 years is recommended for patients with Ph-positive ALL not undergoing allogeneic HSCT in first remission (CQ8).

For Ph-negative ALL, pediatric-type chemotherapy is recommended for adolescents and young adult (AYA) patients (generally < 40 years). Regimens with high-dose methotrexate are recommended as adult chemotherapy protocols for ALL patients aged 40–64 years. When using pediatric-type chemotherapy for adults, drug doses must be adjusted based on the patient's age (CQ11). There is currently no clear evidence indicating that T-cell ALL (T-ALL) and B-cell ALL (B-ALL) should be treated with separate regimens (CQ10). LBL belongs to the same category as ALL in the 2017 WHO classification, and the same treatments for ALL are recommended for LBL (CQ12).

Once complete remission (CR) is achieved, CNS prophylaxis with intrathecal anticancer drugs and high-dose methotrexate or high-dose cytarabine is essential regardless of Ph chromosome status or age. Cranial irradiation is acceptable for high-risk patients (CQ3). For Ph-negative ALL in first remission, continuation of chemotherapy is recommended in patients treated with a pediatric-type protocol, but allogeneic HSCT should be considered for patients with unfavorable prognostic factors (CQ5). As reduced-intensity conditioning (RIC) for allogeneic HSCT has comparable outcomes to myeloablative conditioning (MAC) in patients 45 years and older, an appropriate conditioning regimen should be selected with due consideration to the trade-offs between treatment-related toxicity and relapse risk (CQ6). Maintenance therapy is recommended when not performing allogeneic HSCT in first remission (CQ8).

Assessment of MRD at or after CR achievement is important for predicting relapse. Patients with MRD $\geq 0.01\%$ after induction therapy are at high risk of relapse, and the optimal timing of the second and subsequent MRD assessments depends on the treatment regimen used (CQ4).

Standard therapy for elderly (≥ 65 years) patients with Ph-negative ALL is still under development. The options are combination chemotherapy or palliative steroid therapy depending on the patient's condition (CQ13).

Reinduction therapy for relapsed ALL should be selected with consideration to prior therapy. Late relapse can be treated with the same regimen used for initial induction therapy. For relapsed B-ALL, blinatumomab is recommended if CD19-positive and inotuzumab ozogamicin if CD22-positive. For relapsed Ph-positive ALL, it is reasonable to switch to dasatinib or ponatinib if the patient previously received imatinib, and to ponatinib if the patient previously received dasatinib. Nelarabine is an additional treatment option for relapsed T-ALL. Chimeric antigen receptor (CAR) T-cell therapy is another option for patients with relapsed CD19-positive B-ALL who are 25 years or younger and were unable to achieve second remission or relapsed after allogeneic HSCT (CQ9).

Explanation

Before TKIs became available, all types of ALL, including Ph-positive ALL, were treated with the same chemotherapy regimens. Therefore, many studies have reported treatment outcomes of adding the first-generation TKI imatinib to conventional chemotherapy. All studies showed that both hematologic complete remission (HCR) and overall survival (OS) were promising compared with the pre-TKI era [1–6]. Studies have also investigated which chemotherapy regimens to combine: an RCT that compared intensive chemotherapy against reduced-intensity chemotherapy showed that the significantly higher rate of early death during induction therapy among patients who received intensive chemotherapy affected treatment outcomes [7]. Second-generation TKIs were subsequently developed and investigated in clinical trials, most of which used dasatinib. Combination of intensive chemotherapy with dasatinib rather than imatinib tended to improve outcomes, but there is currently no evidence that dasatinib is superior to imatinib in RCTs [8–10]. As Ph-positive ALL is relatively common among the elderly, and a certain rate of early death is inevitable when using a TKI plus intensive chemotherapy, induction with a TKI plus a steroid alone has also been investigated [11, 12]. A Japanese study of a similar treatment in non-elderly patients showed excellent results, with no early deaths and a 100% HCR rate [13]. Although dasatinib is not covered by Japanese NHI for newly diagnosed Ph-positive ALL, it is often used in practice because it has stronger BCR-ABL1 inhibitory activity than imatinib and effects against *ABL1* gene mutations, except for such as T315I and E255V. The treatment outcomes of combination dasatinib with blinatumomab, a bispecific T-cell engager antibody against CD19 and CD3, has been reported recently [14] and "chemotherapy-free" therapy might be established in Ph-positive ALL as well. Blinatumomab is currently only covered by Japanese NHI for relapsed or refractory disease. The third-generation TKI ponatinib retains its potent inhibitory effects against mutations such as T315I, a variant *BCR::ABL1* mutation that is

CQ1 Which TKIs are recommended for newly diagnosed Ph-positive ALL?

Recommendation grade: Category 2A
Second- and later-generation TKIs are often used, but some are not covered by Japanese National Health Insurance (NHI) for newly diagnosed patients. First-generation TKIs have never been compared against second- and third-generation TKIs in a randomized controlled trial (RCT).

resistant to other TKIs. Combination of intensive chemotherapy with ponatinib rather than imatinib or dasatinib produces superior outcomes to previous therapies, including an earlier molecular response (MR), which suggests that even currently recommended HSCT may be avoidable [15, 16]. However, it should be noted that the ponatinib dosage was amended in this protocol due to adverse events. A trial that investigated combination of ponatinib with a steroid alone in elderly patients or those unfit for intensive chemotherapy showed that ponatinib dose reduction may be necessary in this group [17]. Ponatinib is also not covered by Japanese NHI for newly diagnosed Ph-positive ALL. The results of RCTs between TKIs have not been reported. When selecting a TKI, it is necessary to understand the efficacy and adverse event profiles of each TKI and to consider age and comorbidities.

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CQ2 What primary therapy is recommended for elderly patients (≥ 65 years) with Ph-positive ALL?

Recommendation grade: Category 2A Induction with a TKI plus a steroid is recommended for elderly patients with Ph-positive ALL.
Recommendation grade: Category 2A When possible, reduced-intensity consolidation and maintenance chemotherapy is recommended in addition to TKI therapy.

Explanation

In a Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) study of induction with imatinib plus chemotherapy in patients aged 55 years and older, CR was achieved in 72% of patients [1]. In a German Multicenter Study Group for Adult ALL (GMALL) study that compared single-agent imatinib against combination chemotherapy in patients aged 55 years and older, the CR rate was significantly better with single-agent imatinib (96.3% vs. 50.0%). There were also fewer adverse events in the single-agent imatinib group, demonstrating the efficacy of single-agent imatinib induction [2]. In a Gruppo Italiano Malattie Ematologiche dell'Adulto (GIMEMA) study of 800 mg imatinib alone in elderly patients, the CR rate was 100% but molecular remission was only achieved in 1 of 27 patients [3]. Combination of TKIs with steroids has also been investigated. In the GIMEMA LAL1205 trial, induction with dasatinib 140 mg plus a steroid resulted in a 100% CR rate, with approximately 20% of patients achieving a *BCR::ABL1* reduction to $< 10^{-3}$, though it should be noted that the trial population was relatively young (median age 53.6 years) [4]. Based on these reports, induction with a TKI plus a steroid is recommended for elderly patients with Ph-positive ALL. In the GIMEMA LAL1811 trial, in which patients with a median age of 66.5 years (approximately 80% ≥ 60 years) received induction therapy with ponatinib 45 mg and prednisolone, the 24-week CR rate (86.4%) and molecular remission rate (40.9%) were lower than the rates previously reported for imatinib and dasatinib. Because of its high incidence of cardiovascular adverse events in the regimen, further investigation is required to determine the optimal dosage of ponatinib (Japanese NHI only covers ponatinib in Ph-positive ALL patients for relapsed or refractory B-ALL) [5].

Single-agent TKI therapy has limitations in the post-remission setting, as illustrated by the high relapse rate (17/19) in patients who continued single-agent TKI therapy in the GIMEMA LAL1205 trial [4]. Relapsed patients had a high rate of T315I *BCR::ABL1* mutations, which confer resistance to dasatinib. In a European Working Group for Adult ALL (EWALL) trial, a patient population with a median age of 69 years received dasatinib plus reduced-intensity chemotherapy for induction, consolidation, and maintenance, and subsequently continued dasatinib. The CR rate was 96%, 5-year relapse-free survival (RFS) rate was 28%, and OS rate was 36%, demonstrating the benefit of treatment with a TKI plus reduced-intensity chemotherapy in elderly patients [6]. In the Cancer and Leukemia Group B (CALGB) 10,701 study, a patient population with a median age of 60 years received dasatinib plus chemotherapy with dexamethasone, followed by post-remission therapy with reduced-intensity chemotherapy. The 5-year disease-free survival (DFS) rate was 34% and OS rate was 46% [7]. On the basis of these reports, consolidation and maintenance with a TKI plus reduced-intensity chemotherapy is recommended for elderly patients when possible. Drug selection and doses for reduced-intensity chemotherapy should be determined with consideration to factors such as the patient's age and performance status, but as one example, the EWALL consolidation protocol consists of dasatinib 100 mg plus L-asparaginase 10,000 U/m^2 and methotrexate 1 g/m^2 in cycles 1, 3, and 5, and cytarabine 1 g/m^2 every 12 h every other day for 3 day in cycles 2, 4, and 6.

A recent study investigated 2 to 3 cycles of blinatumomab after induction with dasatinib plus a steroid as a chemotherapy-free approach. The CR rate was 98%, and a molecular response of 2 log or greater was achieved in 29% of patients after induction with dasatinib and 60% after 2 cycles of blinatumomab. OS and DFS rates at 18 months were excellent 95% and 88%, respectively, making blinatumomab a promising treatment option for elderly patients (Japanese NHI covers blinatumomab for relapsed or refractory B-ALL) [8].

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adult ALL patients reduced the CNS relapse rate to 2.3%, but the treatment-related mortality rate in patients 45 years and older was as high as 23% [3]. Considering the only 4% of CNS recurrence rate in Hyper-CVAD/MA with IT protocol, which includes 7% of patients with CNS involvement at the time of initial onset, and irradiation affects the CNS, the indication for intracranial irradiation should be carefully considered [2]. In an RCT of high-dose versus intermediate-dose methotrexate by the Japan Adult Leukemia Study Group (JALSG ALL202-O trial), cranial irradiation (20–24 Gy) was given solely to patients with CNS involvement at diagnosis [4]. The overall CNS relapse rate was only approximately 1%, with one relapse in the high-dose methotrexate group and three in the intermediate-dose methotrexate group (no significant difference between groups), showing that cranial irradiation is an acceptable treatment for patients with CNS involvement. In a GIMEMA trial, AYA ALL patients classified with high risk based on cytogenetic abnormalities, MRD, and response to early prednisolone therapy received 18 Gy of cranial irradiation, and those with CNS involvement at initial presentation received 24 Gy. The CNS relapse rate was 5% (4/76), demonstrating that optimizing the intensity of CNS prophylaxis based on the disease risk leads to favorable outcomes [5]. In conclusion, cranial irradiation for ALL should be in the range of 18 to 24 Gy, and should only be considered for patients who have CNS involvement at diagnosis or are at high risk. More careful consideration is required for patients aged 45 years and older due to risk of adverse events.

In an RCT that compared single-agent intrathecal methotrexate against intrathecal triple therapy with added

CQ3 What CNS prophylaxis is recommended for treatment of adult ALL?

Recommendation grade: Category 2A Intrathecal anticancer drugs and high-dose methotrexate or high-dose cytarabine is recommended for all adult ALL patients.
Recommendation grade: Category 2B Cranial irradiation is an acceptable method of CNS prophylaxis for high-risk patients.

Explanation

Without CNS prophylaxis, the CNS relapse rate in adult ALL is a high 30%. However, intrathecal anticancer drugs and intensified chemotherapy with high-dose methotrexate or high-dose cytarabine have been shown to significantly reduce the CNS relapse rate [1, 2]. Treatment with a pediatric ALL regimen, including 18 Gy of cranial irradiation, for cytarabine and prednisolone in children with standard-risk ALL, patients who received the intrathecal triples had a significantly lower 6-year CNS relapse rate (5.9% vs. 3.4%), but higher rates of bone marrow and testicular relapse, which resulted in significantly lower 6-year OS rate (94.4% vs. 90.3%) [6]. No comparative trials of intrathecal regimens have been conducted for adult ALL.

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to identify leukemic cells with abnormal immunophenotypes [1, 2], RQ-PCR to identify leukemia-specific fusion genes (e.g., *BCR::ABL1*) and Ig/TCR gene rearrangements, and next-generation sequencing to identify Ig/TCR gene rearrangements [3, 4]. Japanese NHI covers MRD assessment based on leukemia-specific fusion genes, and has also covered up to two rounds of MRD assessment based on Ig/TCR gene rearrangements (RQ-PCR) since 2019. This method requires submission of a specimen for patient-specific primer generation before the start of treatment, and can generally detect MRD with a sensitivity of $< 1 \times 10^4$ in a good-quality specimen.

Many clinical studies have examined the correlation between MRD and prognosis, and meta-analyses of these studies are also being published. In most of the clinical studies included in these meta-analyses, the MRD cutoff was 0.01%. In a meta-analysis of 16 clinical studies in adults (n = 2076 patients), 20 in children (n = 11,249), and 3 in both adults and children (n = 312) [5], the hazard ratio (HR) for event-free survival (EFS) in MRD-negative adult patients was 0.28 (95% confidence interval [CI] 0.20–0.39), with 10-year EFS at 21% in the MRD-positive group versus 64% in the MRD-negative group. Comparison by timing of MRD assessment showed that the HR was 0.33 (95% CI 0.24–0.44) for patients who were MRD-negative after induction and 0.25 (95% CI 0.18–0.36) for those after consolidation, indicating a strong correlation of MRD negativity with prognosis at both time points. Another meta-analysis

CQ4 What are the recommended methods, timing, and cutoffs for MRD assessment in adult ALL in remission?

Recommendation grade: Category 1 Leukemia-specific fusion gene detection by real-time quantitative polymerase chain reaction (RQ-PCR) and immunoglobulin heavy chain (Ig)/T cell receptor (TCR) gene rearrangement testing are recommended.
Recommendation grade: Category 2A MRD ≥ 0.01% after induction is associated with high risk of relapse. Depending on the treatment regimen used, the optimal timing of second and subsequent MRD assessments varies, with some possibilities being after induction or after consolidation. Optimal timing of MDS assessment and threshold should be investigated in clinical trials for each therapeutic intervention. In practice, it is recommended to perform the first MRD assessment after induction.

Explanation

MRD assessment is testing to quantify leukemic cells below the level detectable by morphologic identification.

A method with sensitivity of at least $< 1 \times 10^4$ (< 0.01%) for identification of leukemic cells in bone marrow mononuclear cells is appropriate for MRD assessment. Methods used worldwide are 6-color or higher-color flow cytometry of 23 studies of adult B-ALL showed that MRD negativity was associated with RFS (HR 2.34, 95% CI 1.91–2.86) and OS (HR 2.19, 95% CI 1.63–2.94) and strongly correlated with prognosis regardless of whether the timing of MRD assessment was within 3 months after treatment initiation (HR 2.60, 95% CI 2.05–3.31) or later than 3 months after treatment initiation (HR 2.23, 95% CI 1.67–2.97) [6]. A Japanese study also reported the results of an assessment for

MRD in 51 patients with Ph-negative ALL. The 15 patients who were MRD-negative after induction had a significantly better 3-year DFS rate than the 30 patients who were MRD-positive after induction (73% vs. 41%, $p = 0.018$), and the 11 patients who became MRD-negative after the first consolidation cycle also had an inferior 3-year DFS rate (45%) to those who were MRD-negative after induction [7]. Many clinical studies have used MRD $< 10^{-3}$ after induction as a factor for treatment stratification [8].

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CQ5 Is allogeneic HSCT recommended for ALL in first remission (both Ph-negative and Ph-positive)?

Recommendation grade: Category 2A
For Ph-negative ALL in first remission, continuation of chemotherapy is recommended in patients treated with a pediatric-type protocol, but allogeneic HSCT should be considered for patients with unfavorable prognostic factors.
Allogeneic HSCT is recommended for Ph-positive ALL in first remission.

Explanation

The indication for HSCT in patients with ALL in first remission has been evaluated in prospective comparative trials employing genetic randomization, meaning that patients with an HLA-matched donor were assigned to receive allogeneic HSCT and patients without a donor were assigned to receive autologous HSCT or chemotherapy. It must be noted that such studies include patients who did not receive their assigned treatment because they employ intent-to-treat analysis, in which groups for analysis are determined by assigned group (i.e., donor group vs. no donor group) to avoid bias that would arise from grouping by actual treatment received. An increasing number of retrospective analyses are comparing age-matched chemotherapy against allogeneic HSCT.

The prognosis of Ph-negative ALL has improved with the widespread adoption of pediatric-type chemotherapy protocols. A large study that compared patients aged 16–39 years who received pediatric-type chemotherapy (per the CALGB10403 protocol) or were enrolled in the Center for International Blood and Marrow Transplant Research (CIBMTR) registry showed that pediatric chemotherapy yielded superior OS, DFS, and non-relapse mortality (NRM) to allogeneic HSCT with MAC [1]. In the GRAALL-2003 and GRAALL-2005 trials, which included patients up to 55 years, genetic randomization was performed based on HLA-matched donor availability in patients with unfavorable prognostic factors, and allogeneic HSCT in first remission was found to offer no benefit over no HSCT [2]. A joint study by the JALSG and Japanese Society for Transplantation and Cellular Therapy (JSTCT) analyzed data from patients in the JALSG registry who received chemotherapy and patients in the JSTCT registry (TRUMP) who underwent HSCT from an HLA-matched related donor or 8/8 allele-matched unrelated donor. The 5-year DFS rate with chemotherapy was comparable to or better than that with HSCT in patients aged 16 to 24 years (70.4% vs. 62.8%) and patients aged

25 to 65 years (57.0% vs. 60.7%) [3]. Chemotherapy tends to be favored in first remission, due to the drop in quality of life that occurs after HSCT. However, allogeneic HSCT is better in patients with factors such as the poor-risk t(4;11), ≥ 5% leukemic cells remaining in the bone marrow during the first week, or requiring salvage therapy to achieve remission [2]. MRD positivity (0.1% or ≥ 0.01%) is also considered an indication for HSCT because these patients have a poor prognosis with chemotherapy [4].

Chemotherapy outcomes for Ph-positive ALL are improving dramatically due to the adoption of TKIs, but many trials include allogeneic HSCT in first remission as part of the treatment protocol, which complicates comparison with patients who did not undergo HSCT. In many of these trials, HSCT recipients had a better prognosis. In the Japanese Ph + ALL 208 trial, the 3-year OS rate was 74% in patients who underwent allogeneic HSCT in first remission versus 48% in those who did not undergo HSCT [5]. Two other meta-analyses have been published to date [6, 7]. Although there is some overlap in the studies analyzed, both showed that DFS and RFS were better with HSCT. In the Group for Research on Adult Acute Lymphoblastic Leukemia Philadelphia positive (GRAAPH)-2005 trial, which was the largest trial (n = 254) employing genetic randomization, outcome was significantly better with allogeneic HSCT than without HSCT [8]. Based on these results, this guideline recommends that allogeneic HSCT be performed in first remission. Use of imatinib or dasatinib in TKI therapy does not affect the recommendation for allogeneic HSCT, since there seems to be no difference in prognosis between the two groups.

However, some retrospective analyses have shown no difference in prognosis between patients with favorable prognosis who underwent allogeneic HSCT and those who continued chemotherapy. The GRAAPH-2005 trial showed that only patients with a baseline WBC count ≥ 30,000/μL gained a benefit from allogeneic HSCT, as it produced no difference in outcome among patients with a baseline WBC count < 30,000/μL regardless of whether a patient underwent HSCT or not. Prognosis was poor in patients with a < 4 log reduction in *BCR::ABL1* in bone marrow after 2 chemotherapy cycles who did not undergo HSCT, but was comparable between patients with a < 4 log reduction who underwent HSCT, patients with a ≥ 4 log reduction who did not undergo HSCT, and patients with a ≥ 4 log reduction who underwent HSCT [8]. A Chinese study showed similar results: RFS was comparable between HSCT recipients and non-recipients (88.2% vs. 83.9%) in the low-risk group who had a baseline WBC count < 30,000/μL at initial presentation and a ≥ 3 log reduction in *BCR::ABL1* expression after 2 consolidation cycles [9].

Since it can reasonably be assumed that the population of HSCT recipients in previously published studies would be skewed toward patients with good performance status and organ reserve, further research is warranted to determine the indications for HSCT.

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CQ6 Is MAC or RIC recommended for allogeneic HSCT in first remission of ALL?

Recommendation grade: Category 2B

As RIC has comparable outcomes to MAC in ALL patients aged 45 years and older, an appropriate conditioning regimen should be selected with due consideration to the trade-offs between treatment-related toxicity and relapse risk.

A MAC regimen consisting of cyclophosphamide, 12 Gy of total body irradiation (TBI), and intermediate-dose etoposide is beneficial for ALL patients younger than 45 years without comorbidities.

Explanation

In a European Society for Blood and Marrow Transplantation (EBMT) study that retrospectively compared HLA-matched sibling HSCT in first or second remission in ALL patients aged 45 years and older, the 2-year NRM rate was significantly higher with MAC than RIC (29% vs. 21%, $p = 0.03$), but the 3-year relapse rate was significantly higher with RIC than MAC (47% vs. 31%, $p < 0.001$), and the 3-year survival rate was comparable between RIC and MAC (48% vs. 45%). Multivariate analysis also showed that RIC was an independent factor associated with low transplant-related mortality and high relapse risk [1]. In an analysis by the Adult ALL Working Group of the Japan Society for Hematopoietic Cell Transplantation (JSHCT), which included related, unrelated, and cord blood transplants, 3-year NRM was comparable between RIC and MAC (36% vs. 38%) and the 3-year relapse rate was significantly higher with RIC (26% vs. 15%, $p = 0.008$), but the 3-year survival rate was comparable (53% vs. 51%). Unlike in the European study, multivariate analysis did not identify RIC as an independent factor associated with treatment-related mortality, relapse, or survival rates. In patients aged 55 years and older with HLA-mismatched donors, OS was significantly better with RIC [2].

In another analysis by the Adult ALL Working Group of the JSHCT, treatment outcomes were comparable between RIC and MAC in Ph-positive ALL patients aged 50 years and older who became MRD-negative, but were significantly better with RIC in patients with poor performance status and a high HCT-specific comorbidity index (HCT-CI) [3].

As RIC regimens for ALL patients aged 45 years and older, fludarabine-based regimens with added busulfan, melphalan, or TBI are widely used. There was no superiority or inferiority among the three RIC regimens, and all had comparable outcomes [4].

A Japanese study retrospectively compared the effect of adding intermediate-dose etoposide to cyclophosphamide/TBI in MAC regimens for ALL [5]. NRM was comparable between groups, but the etoposide/cyclophosphamide/TBI group had a significantly lower relapse rate (HR 0.75, $p = 0.05$) and significantly better leukemia-free survival (LFS) (HR 0.76, $p = 0.01$). In subgroup analysis, LFS improved in adverse-risk patients in first remission as well as patients in second or subsequent remission. This may be a beneficial conditioning regimen for ALL patients younger than 45 years who do not have comorbidities.

No study has yet compared the benefit of RIC/MAC by MRD status (i.e., disease risk), other than in Ph-positive ALL. In addition, all of these were retrospective studies using registry data, and no prospective studies exist. However, Japan has the advantage of a large body of evidence currently being generated. At present, it is necessary to carefully consider the trade-offs of RIC/MAC, namely, treatment-related mortality and relapse rate, to select a conditioning regimen suited to each individual patient.

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was significantly lower in group A (40% vs. 69%, $p=0.046$), but neither maintenance rate of hematologic remission (81% vs. 78%) nor 5-year OS rate (80% vs. 74.5%) differed between groups. In the Japanese JALSG Ph + ALL213 trial, patients who underwent allogeneic HSCT after receiving dasatinib-combined chemotherapy received prophylactic dasatinib therapy when they were MRD-positive before HSCT ($n=14$) or preemptive dasatinib therapy when they were MRD-negative before HSCT ($n=44$) [2]. The study's

CQ7 Is post-transplantation TKI maintenance therapy recommended for Ph-positive ALL?

Recommendation grade: Category 2A Preemptive TKI therapy is recommended when MRD is detected after allogeneic HSCT, but prophylactic TKI maintenance in MRD-negative patients is not recommended.

Explanation

TKI maintenance therapy after allogeneic HSCT for Ph-positive ALL can be either prophylactic (initiated while the patient is MRD-negative) or preemptive (initiated when the patient becomes MRD-positive). Although no RCT has validated the efficacy of broadly defined TKI maintenance therapy including preemptive therapy, prospective single-arm trials have shown that broadly defined TKI maintenance therapy after allogeneic HSCT produced better outcomes than those observed in historical controls [1, 2], and a retrospective cohort study showed that outcomes were better in patients who underwent TKI maintenance therapy versus those who did not [3]. Although it is unclear to what extent TKI maintenance therapy contributed to improved outcomes in these studies because patients who received TKI maintenance also received TKI combination therapy before HSCT, these results illustrate a consistent trend toward better outcomes with TKI maintenance. Thus, TKI maintenance therapy should be started in patients who do not become MRD-negative after allogeneic HSCT, or after negative-to-positive conversion. In this case, *ABL1* mutation analysis should ideally be performed to select the appropriate TKI (however, *ABL1* mutation analysis is not covered by Japanese NHI).

One RCT compared the relative benefits of prophylactic and preemptive TKI maintenance therapy [4]. Fifty-five Ph-positive leukemia patients underwent allogeneic HSCT in CR and were assigned to receive prophylactic imatinib (group A, $n=26$) or receive preemptive imatinib after becoming MRD-positive (group B, $n=29$). The MR rate

authors decided not to recommend prophylactic dasatinib, because few patients ($n=6$) actually received dasatinib therapy in the preemptive therapy group, all of them achieved molecular remission again, and a higher incidence (6 of 8 patients) of severe adverse events associated with dasatinib was observed in the prophylactic group. Based on such evidence, prophylactic TKI maintenance is not recommended for patients who are MRD-negative after allogeneic HSCT.

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CQ8 Is maintenance therapy recommended for ALL patients not undergoing HSCT in first remission?

Recommendation grade: Category 1 (Ph-negative), Category 2A (Ph-positive) Maintenance therapy is recommended for patients not undergoing HSCT in first remission. Long-term TKI therapy is recommended for Ph-positive patients.

Explanation

In the 1960s, an RCT in pediatric ALL demonstrated the benefit of maintenance therapy compared with discontinuation of treatment [1]. Post-remission therapy was not satisfactory in this study because maintenance therapy was performed immediately after induction therapy, which makes it difficult to judge the need for maintenance therapy in the context of current standard of care based on this study alone. However, several subsequent studies also confirmed the need for maintenance therapy. For example, a Japanese study in pediatric ALL investigated dosing methods for mercaptopurine and methotrexate in maintenance therapy by randomizing patients to receive intermittent intermediate doses or continuous low doses and found that intermittent dosing yielded a better 5-year continuous complete remission rate (72.1% vs. 49.7%, $p < 0.05$) [2].

Similar findings have been obtained for adult ALL. In a CALGB study in which patients were treated with a protocol that did not include maintenance therapy, the study was terminated early because the interim analysis showed that duration of remission was clearly lower than in the past CALGB studies (that included maintenance therapy for more than one year), demonstrating the need for maintenance therapy [3]. In addition, in a joint study by the UK Medical Council and Eastern Cooperative Oncology Group, 1929 ALL patients in remission were assigned to receive allogeneic HSCT if they had an HLA-matched related donor, or randomized to autologous HSCT without maintenance therapy or chemotherapy including consolidation and maintenance therapies if they did not. Both groups received intensive therapy with high-dose methotrexate. Patients who received autologous HSCT had a significantly worse 5-year OS rate (46% vs. 37%, $p = 0.03$) [4]. This study yet again demonstrates the need for maintenance therapy. On the basis of evidence from these studies, maintenance therapy is considered necessary for patients with Ph-negative ALL who are not undergoing HSCT in first remission.

Many studies have investigated imatinib plus chemotherapy for Ph-positive ALL since the introduction of imatinib. All these studies showed that imatinib plus chemotherapy yielded marked improvement in CR rate, the percentage of patients undergoing allogeneic HSCT in first remission, and OS compared with previous therapies. However, OS among patients who did not undergo allogeneic HSCT differed greatly between studies. Studies in which maintenance therapy with imatinib was concluded after 2 to 3 years had a high relapse rate (78–87%) among patients who did not undergo HSCT [5, 6]. In contrast, studies in which treatment with imatinib was continued for 5 years or indefinitely showed much higher DFS rates of 42.7% (3 years) [7] and 43% (5 years) [8], respectively, even among patients who did not undergo allogeneic HSCT. On the basis of evidence from these studies, it is recommended to perform maintenance therapy with a TKI in Ph-positive ALL patients who do not undergo allogeneic HSCT, and to continue TKI therapy for at least 5 years from treatment initiation. It is currently unknown whether TKI therapy can be stopped at any point, for example, based on assessment of MRD.

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regimen (cyclophosphamide, vincristine, doxorubicin, and dexamethasone). The same regimen used for the initial induction therapy is also a good option if the case is a late relapse. Hyper-CVAD (or modified hyper-CVAD) therapy is a good choice to combine with the novel agents discussed below because we can find evidence for such therapy.

Inotuzumab ozogamicin is a conjugate of humanized anti-CD22 monoclonal antibody, which is a B-cell-specific antigen, with calicheamicin, which is a cytotoxic compound. For relapsed or refractory precursor B-ALL, it significantly improved the CR rate in an RCT (81% vs. 29%). However, caution must be taken for veno-occlusive disease (VOD), as VOD was observed in 11% of all patients and in 21%

CQ9 What are the recommended reinduction therapy options for relapsed ALL, and when should CAR T-cell therapy be considered?

Recommendation grade: Category 2B Reinduction therapy for relapsed ALL should be selected with consideration to prior therapy. Late relapse can be treated with the same regimen used for initial induction therapy.
Recommendation grade: Category 1 For relapsed B-ALL, blinatumomab is recommended for CD19-positive and inotuzumab ozogamicin for CD22-positive disease.
Recommendation grade: Category 2A For relapsed Ph-positive ALL, it is reasonable to switch to dasatinib or ponatinib if the patient previously received imatinib, and to ponatinib if they previously received dasatinib.
Recommendation grade: Category 2B Nelarabine is an additional treatment option for relapsed T-ALL.
Recommendation grade: Category 2A CAR-T cell therapy is another option for some relapsed/refractory CD19-positive B-ALL patients aged 25 years and younger (see Explanation for specific indications).

Explanation

Relapsed adult ALL generally has a poor prognosis. It can be a curative treatment, and thus, is a recommended treatment strategy to achieve second remission and receive HSCT; however, not many patients can undergo allogeneic HSCT in second remission due to low second remission rates and short duration of second remission. In an analysis of 421 patients who had a first relapse in the LALA-94 trial, 44% achieved second remission, and 14% were able to undergo allogeneic HSCT in second remission [1]. For the selection of reinduction therapy, it is recommended to select a regimen including drugs that were not used in the initial therapy of the patient from regimens that are broadly used for initial induction therapy of ALL, such as 5-drug combination therapy (doxorubicin, vincristine, L-asparaginase, cyclophosphamide, and prednisolone) and the hyper-CVAD

of patients who underwent allogeneic HSCT after treatment with inotuzumab ozogamicin [2]. Blinatumomab is a bispecific T-cell engager, in which monoclonal antibodies against the B-cell-specific antigen, CD19, and the T-cell-specific antigen, CD3, are joined by a linker. It induces a T-cell-mediated immune response by cross-linking neoplastic B cells with T cells. For relapsed or refractory B-ALL, it significantly improved the CR rate in an RCT (34% vs. 16%) [3]. Blinatumomab is an excellent bridging therapy to allogeneic HSCT because it is relatively safe due to its mild myelosuppression. It may also address the problem of VOD in allogeneic HSCT after treatment with inotuzumab ozogamicin, as pre-HSCT consolidation with blinatumomab after induction with inotuzumab ozogamicin plus chemotherapy has been shown to reduce the incidence of VOD [4].

BCR::ABL1 mutations conferring imatinib resistance are often found in relapsed Ph-positive ALL during or

after imatinib therapy. Dasatinib, a second-generation TKI, retains its inhibitory activity against many *BCR::ABL1* genes with imatinib-resistant mutations, except for T315I. In a phase II study of dasatinib monotherapy in patients with Ph-positive ALL who relapsed on imatinib, the hematologic response rate was 42% and patients were able to maintain their response for several months [5]. This suggests that dasatinib may be efficacious for some patients who acquired mutations conferring imatinib resistance. Ponatinib, a third-generation TKI, retains its inhibitory activity against *BCR::ABL1* with the dasatinib-resistant T315I mutation. Ponatinib was demonstrated efficacious in a trial of patients refractory or intolerant to dasatinib or nilotinib or patients positive for *BCR::ABL1* T315I [6]. *ABL1* mutation analysis should ideally be performed at the time of relapse to confirm the presence and type of TKI resistance mutations to inform TKI selection, but *ABL1* mutation analysis is currently not covered by Japanese NHI. Inotuzumab ozogamicin and blinatumomab have proven efficacy for treatment of relapsed Ph-positive ALL, and can be combined with a TKI.

Nelarabine therapy has been demonstrated efficacious in patients with relapsed and refractory T-ALL. In a phase II study by CALGB, the overall response rate in heavily pretreated T-ALL patients was 41% [7].

CAR-T-cell therapy involves infusion of autologous T cells transfected with a chimeric antigen receptor gene (CAR-T cells), and CD19 CAR-T cell, tisagenlecleucel, is approved for some relapsed/refractory CD19-positive B-ALL patients aged 25 years and younger. The indications are for refractory CD19-positive B-ALL patients who failed to achieve remission after initial treatment with at least two standard chemotherapy regimens, or relapsed patients who failed to achieve re-remission after treatment with at least one chemotherapy regimen, are ineligible for allogeneic HSCT, or relapsed after allogeneic HSCT. In a clinical trial, tisagenlecleucel showed high efficacy for relapsed or refractory CD19-positive B-ALL (CR rate 81%) but caused specific severe adverse events such as cytokine release syndrome, which occurred in 77% of patients [8]. Consequently, this treatment is only available at selected and registered facilities in Japan for safety reasons. Since CAR T-cell therapy is extremely expensive, strict compliance with insurance coverage requirements must be ensured when deciding on this treatment. The turnaround time for the finished product to arrive after shipping of apheresis products needed for cell production is about 6 weeks, so it is important to make arrangements with the treating facility as soon as possible.

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CQ10 For newly diagnosed Ph-negative ALL, is it recommended to treat T-ALL and B-ALL with similar regimens?

Recommendation grade: Category 2B
Although T-ALL can be a treatment stratification factor, separate regimens from those used for B-ALL have not been established.

Explanation

T-ALL is considered to have a poorer prognosis than B-ALL in children, but no clear difference has been observed in adults [1]. However, a few factors need to be taken into consideration, including that a large proportion of children with B-ALL have favorable prognostic factors and that a large number of adults with B-ALL have Ph-positive ALL, which was particularly difficult to treat in the pre-TKI era [2]. T-ALL and B-ALL are treated with the same regimens in adults, including elderly adults, and no large clinical trials have investigated separate regimens for T-ALL. Recent research has shown that pediatric-style protocols are better than previously used adult protocols for the AYA age group [3], which led to clinical trials attempting pediatric-style protocols in older than AYA age groups. Compared with adult protocols, pediatric-style protocols use higher doses of steroids, vincristine, and L-asparaginase, and are more likely to include CNS prophylaxis. They are also characterized to incorporate treatment stratification, including HSCT, by baseline prognostic factors, response to primary treatment, and post-remission MRD status. Even in children, T-ALL is often treated with the same protocols as B-ALL. However, some protocols stratify T-ALL as poor-risk because patients with T-ALL tend to be older at onset than those with B-ALL and have fewer good-risk genetic subtypes, a markedly elevated WBC count at diagnosis, and extramedullary masses such as anterior mediastinal masses [4, 5]. No previous studies of the use of pediatric-style protocols for adult patients were RCTs and some did not consider T-ALL as an independent unfavorable prognostic factor in stratification, but these studies showed superior treatment outcomes to those of previous adult protocols, and no difference in outcomes between B-ALL and T-ALL [6–10]. For treatments for T-ALL, some RCTs have evaluated the efficacy of high-dose methotrexate plus nelarabine, which is an effective drug against T-ALL [11, 12]. Among patients treated with a pediatric-style protocol in a trial in AYAs ($\leq$31 years old), Capizzi style methotrexate therapy, in which methotrexate is started at a low dose and gradually increased, was superior to high-dose methotrexate, and patients who received nelarabine had better treatment outcomes. One study reported treatment outcomes of adding nelarabine to an adult protocol, but showed no survival benefit compared with existing regimens [13]. It should be noted that there are insurance coverage issues regarding the use of nelarabine for newly diagnosed ALL. Molecular mechanisms of pathogenesis are gradually becoming clearer for ALL. T-ALL differs from B-ALL not only in its molecular pathology and clinical features, but also in terms of responsiveness to treatment and which drugs are effective. Consequently, it is reasonable to assume that treatment strategies using different drugs for T-ALL and B-ALL will be established in the future.

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Center, which investigated the hyper-CVAD/MA regimen (cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and high-dose cytarabine). In this trial, CR and 5-year OS rates were 94% and 30%, respectively, for patients 40 to 59 years ($n=82$), compared

CQ11 What treatments are recommended for older adult (aged 40 to 64 years) patients with Ph-negative ALL?

Recommendation grade: Category 2A

Adult protocol with high-dose methotrexate is recommended. When pediatric-inspired protocols are used in adults aged 40 to 64 years, drug doses must be adjusted based on age group.

Explanation

No article has summarized chemotherapy for Ph-negative ALL patients aged 40 to 64 years, but Table 1 shows treatment outcomes from studies in adult ALL patients that were published in the mid-2000s or later. The CR rate ranged from 74 to 94% and OS rate from 32 to 60%. Careful interpretation of OS results is required because many clinical trials add HSCT based on prognostic factors, in which case treatment outcomes cannot be attributed to chemotherapy alone.

Clinical trials for this age group used either an adult protocol or a pediatric-inspired protocol. One example of an adult protocol is from a trial by M.D. Anderson Cancer with 80% and 17%, respectively, for patients aged 60 years and older ($n=59$) [1]. Another study that investigated an adult protocol is JALSG ALL97, and a subgroup analysis in Ph-negative ALL patients in this study showed CR and 5-year OS rates of 81% and 39%, respectively, in the subgroup overall, 80% and 38%, respectively, for patients aged 35 to 54 years, and 78% and 26%, respectively, for those aged 55 to 64 years [2]. In the JALSG ALL202-O trial, which investigated addition of high-dose methotrexate to an adult protocol, the CR rate was 86% and 5-year OS was 64% in patients aged 25 to 64 years, which was significantly better than the 5-year OS rate of 48% in the comparator group that received intermediate-dose methotrexate [3].

Table 1 Treatment outcomes for adult patients with ALL

Study name	Year published	Study period	Sample size	Median age (range)	SCT	Ph	Protocol type	Remission rate	OS rate
Hyper-CVAD	2004	1992–2000	288	40 (15–92)	yes	yes	Adult	92%	38% (5 years)
LALA 94	2004	1994–2002	922	33 (15–55)	yes	yes	Adult	84%	33% (5 years)
MRC UKALL XII/ECOG E2993	2005	1993–2003	1521	15–59	yes	yes	Adult	91%	38% (5 years)
GMALL 07/2003	2007	2003–2006	713	34 (15–55)	yes	yes	Pediatric	89%	54% (5 years)
SWOG 9400	2008	1995–2000	200	15–65	yes	yes	Adult 80%	33% (5 years)	SWOG 9400
GRALL-2003	2009	2003–2005	225	31 (15–60)	yes	no	Pediatric	94%	60% (42 months)
JALSG ALL 97	2010	1997–2001	404	38 (15–64)	yes	yes	Adult	74%	32% (5 years)
JALSG ALL202-O (high-dose methotrexate group)	2018	2002–2011	343	43 (25–64)	no	no	Adult	86%	58% (5 years)
GRAALL-2005	2018	2006–2014	787	36 (18–59)	no	no	Pediatric	92%	58.50% (5 years)

One example of a pediatric-inspired regimen for adults is from a study at Princess Margaret Hospital in Canada, which used a modified DFCI91-01 protocol in patients aged 18 to 60 years (median age 37 years). The CR rate decreased with age, from 98 to 86% to 73% across patients aged 35 years or younger, 36 to 49 years, and 50 to 60 years, and 3-year OS rate also decreased, from 83% in patients 35 years or younger to 52% in those 36 years or older [4]. In the French GRAALL-2005 trial, patients aged 18 to 59 years (median 36.1 years) were treated with a pediatric-inspired protocol, and CR rates in patients aged 35 to 44 ($n=171$ patients), 45 to 54 ($n=151$), and 55 to 59 ($n=93$) years were 89.5%, 89.4%, and 79.6%, respectively, with respective 5-year OS rates at 60.3%, 58.0%, and 25.1%. Treatment outcomes were markedly worse in patients aged 55 years and older, and doses for patients aged 45 years and older were changed in subsequent studies due to higher toxicity in that age group [5].

This is why protocols with high-dose methotrexate are recommended as adult regimens, and drug doses must be adjusted based on the patient's age group when pediatric-inspired regimens are used in adults aged 40 to 64 years.

CQ12 What regimens are recommended for LBL without bone marrow involvement?

Recommendation grade: Category 2B The same intensity of chemotherapy used for ALL is recommended for LBL regardless of bone marrow involvement.
Recommendation grade: Category 2B Mediastinal irradiation is effective for T-cell LBL (T-LBL) with mediastinal masses that persist over the course of treatment.

Explanation

LBL responds better to ALL chemotherapy regimens than lymphoma regimens. As ALL regimens, the alternating hyper-CVAD/MA (cyclophosphamide, vincristine, doxorubicin, dexamethasone, high-dose methotrexate, and high-dose cytarabine) [1] and the German Berlin-Frankfurt-Münster (BFM) regimen have been shown to be useful [2]. A pediatric ALL regimen also showed favorable results in adult LBL patients aged 18 to 59 years, with 3-year DFS rate of 72.4% and OS rate of 69.2% [3]. The protocol included CNS irradiation and 2 years of maintenance therapy, and multivariate analysis showed that age (≥ 45 years vs. <45 years) was not a significant risk factor. There is currently no data directly comparing the benefit of alternating hyper-CVAD/MA, BFM, and pediatric ALL regimens.

Mediastinal masses are observed in 70% of T-LBL patients, and irradiation of these masses and of the CNS have been investigated. However, good treatment outcomes have been reported for both adult LBL and pediatric T-LBL with just CNS irradiation and an ALL regimen, without mediastinal irradiation [3, 4]. The previously mentioned clinical trial of a pediatric ALL regimen for adult LBL, in which CNS irradiation was performed prior to maintenance therapy, reported that positive FDG-PET (fluoro-deoxyglucose positron emission tomography) findings after induction therapy were not associated with prognosis [3]. However, one study showed that DFS and OS were significantly lower in FDG-PET-positive patients after induction with the BFM regimen or after 2 cycles of hyper-CVAD [5]. In that study, FDG-PET-positive patients did not receive radiation. Another study showed that 24 Gy of mediastinal irradiation reduced the mediastinal relapse rate to 4.5% in adult LBL patients with residual mediastinal masses on CT after completing 2 cycles of high-dose methotrexate/cytarabine therapy [6].

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In this study, mediastinal mass status at initial presentation did not affect the relapse rate or survival rate. Although no study has compared mediastinal irradiation and CNS irradiation for LBL, mediastinal irradiation of residual masses can be considered superior to prophylactic CNS irradiation considering the negative effects of irradiation on the CNS. The International Lymphoma Radiation Oncology Group (ILROG) guidelines recommend mediastinal irradiation of 30 to 36 Gy, in single fractions of 1.8 to 2 Gy [7].

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Explanation

Very few prospective studies have been conducted in elderly patients (≥ 65 years) with Ph-negative ALL, and standard therapy is still under development. One prospective study was the ALL-OLD07 trial, which was conducted by the Spanish PETHEMA group in patients aged 56 to 79 years (median 66 years), showing a CR rate of 74% and median OS of 12.4 months [1]. Another was the ALL-07FRAIL trial in frail patients aged 57 to 89 years (median 67 years) with a Charlson Comorbidity Index of 4 or higher, which showed a CR rate of 54% and median OS of 7.6 months [2].

Patients aged 65 years and older are more likely to have multiple prior or concurrent diseases than younger patients, and often do not have the appropriate organ function to undergo chemotherapy [3]. Therefore, systemic chemotherapy is associated with higher rates of adverse events and treatment-related mortality in elderly patients. It is important to select treatment intensity based on evaluation of the patient's general condition, including comorbidities, performance status, activities of daily living, and instrumental activities of daily living. Treatment intensity is essentially determined by whether and in what doses myelosuppressive agents are used. Dose reduction of essential ALL chemotherapy drugs such as L-asparaginase, anthracyclines, and myelosuppressive agents should be considered based on general condition.

Low-intensity options include vincristine plus prednisolone [4] and the POMP regimen (prednisolone, vincristine, methotrexate, and mercaptopurine) [5], moderate-intensity options include the GMALL (idarubicin, dexamethasone, vincristine, cyclophosphamide, and cytarabine) [6], PETHEMA-ALLOLD07 (vincristine, dexamethasone, idarubicin, cyclophosphamide, cytarabine, methotrexate, and L-asparaginase) [1], GRAALL (doxorubicin, vincristine, dexamethasone, cytarabine, and cyclophosphamide) [7], and modified DFCI91-01 (dexamethasone, doxorubicin, vincristine, methotrexate, L-asparaginase, mercaptopurine, intrathecal) regimens [8], and high-intensity options include the hyper-CVAD/MA regimen (cyclophosphamide, vincristine,

CQ13 What therapies are recommended for elderly patients (≥ 65 years) with Ph-negative ALL?

Recommendation grade: Category 2B Standard therapy for elderly patients with Ph-negative ALL is still under development. The treatment options should be selected from combination chemotherapy or palliative steroid therapy depending on the patient's condition.

doxorubicin, high-dose methotrexate, and high-dose cytarabine [1 g/m^2]) [9].

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Declarations

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