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GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: I. Leukemia-1. Acute myeloid leukemia (AML)

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Overview

1. Pathology and treatment of AML

Acute myeloid leukemia (AML) is a highly diverse hematologic malignancy characterized by autonomous clonal proliferation of immature myeloid cells that are unable to differentiate or mature normally. Abnormal proliferation of leukemic cells in the bone marrow markedly impairs normal hematopoiesis, causing various symptoms associated with leukopenia, anemia, and thrombocytopenia. It is a serious disease that can lead to death from infection or hemorrhage in a short period of time if not treated properly.

The basic treatment strategy for newly diagnosed AML is intensive curative chemotherapy based on a combination regimen. However, the patient's ability to tolerate organ toxicity and complications of chemotherapy must be carefully and rigorously determined with consideration to their age, organ function, and general condition when deciding whether the patient is a candidate (Table 1).[1,2] Chemotherapy for AML consists of induction therapy and postremission therapy, which is performed after remission is achieved. Patients who do not have a favorable long-term prognosis with chemotherapy alone are candidates for allogeneic hematopoietic stem cell transplantation (HSCT) in first remission.

Patients who do not respond to induction therapy or who relapse after achieving complete remission (CR) require salvage therapy for relapsed or refractory disease. However, as relapsed or refractory disease is unlikely to be cured with chemotherapy alone, these patients are candidates for allogeneic HSCT. Two FLT3 inhibitors (gilteritinib and quizartinib) are available for relapsed or refractory *FLT3*-mutated AML. Both of these drugs require identification of an *FLT3* mutation with an approved companion diagnostic kit prior to use. Note that quizartinib is only indicated for patients with *FLT3*-internal tandem duplication (ITD).

There is no standard definition for the term "elderly," but in Japan, it is commonly used to refer to patients aged 65 years and older. In this guideline, an elderly patient is defined as a person whose physiological age is 65 years or older. Elderly patients with AML cannot be universally treated with chemotherapy of equivalent intensity to that used for younger adult patients due to patient factors such as organ function. Patients with good performance status and sufficient organ function are candidates for chemotherapy, but in general, chemotherapy-related complications tend to be more severe and more frequent in elderly patients with AML. Therefore, careful consideration is required when determining whether an elderly patient is a candidate for intensive chemotherapy.

These criteria can be used as guidance for performing intensive chemotherapy by referencing eligibility criteria defined in phase III clinical trials conducted by the Japan Adult Leukemia Study Group (JALSG) and other such sources. However, eligibility must be determined comprehensively with consideration to the patient's performance status, comorbidities, and other factors.

(From References 1 and 2)

2. Diagnosis and classification of AML

AML is diagnosed when (1) leukemic cells are present in bone marrow (≥ 20% in the 2017 WHO classification and ≥ 30% in the FAB classification), (2) the leukemic cells are of myeloid lineage, and (3) the karyotype and gene mutations of leukemic cells are consistent with AML. It is then classified into subtypes according to the 2017 WHO classification (Table 2).[3] The 2017 WHO classification stipulated that blast percentages should be calculated with all nucleated

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Table 1 Eligibility criteria for intensive chemotherapy

Item	Criterion
Age	< 65 years
Cardiac function	Left ventricular ejection fraction ≥ 50%
Pulmonary function	$PaO_2 \geq 60$ Torr or $SpO_2 \geq 90\%$ (room air)
Hepatic function	Serum bilirubin ≤ 2.0 mg/dL
Renal function	Serum creatinine ≤ 1.5 times the upper limit of reference range
Infection	No uncontrollable concomitant infections

Table 2 The 2017 WHO classification for AML

AML with recurrent genetic abnormalities
AML with t(8;21)(q22;q22.1);RUNX1-RUNX1T1
AML with inv(16)(p13.1q22)or t(16;16)(p13.1;q22);CBFB-MYH11
APL with PML-RARA
AML with t (9;11)(p21.3;q23.3);MLLT3-KMT2A
AML with t (6;9)(p23;q34.1);DEK-NUP214
AML with inv(3)(q21.3q26.2)or (t 3;3)(q21.3;q26.2);GATA2, MECOM
AML (megakaryoblastic)with t(1;22)(p13.3;q13.3);RBM15-MKL1
Provisional entity: AML with BCR-ABL1
AML with mutated NPM1
AML with biallelic mutations of CEBPA
Provisional entity: AML with mutated RUNX1
AML with myelodysplasia-related changes
Therapy-related myeloid neoplasms
AML, NOS
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Pure erythroid leukemia
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis (TAM)
Myeloid leukemia associated with Down syndrome

cells (ANCs) in bone marrow as the denominator, rather than the old formula with non-erythroid cells (NECs) as the denominator. With this change, many cases that would previously have been diagnosed as acute erythroleukemia due to ANC > 50% and myeloblasts ≥ 20% of NEC became classified as myelodysplastic syndrome (MDS) instead. Other minor revisions were also made, including the addition of AML with *BCR::ABL1* fusion gene and AML with mutated *RUNX1* as new provisional entities, and AML with biallelic mutated *CEBPA* and mutated *NPM1* as independent entities from the provisional entities.

Table 3 shows the classification newly proposed in the International Consensus Classification of 2022,[4] and then adopted by the 2022 European Leukemia Net (ELN) recommendations.[5] In this revision, the threshold of blasts percentage for AML was lowered to 10% for patients with AML-defining abnormalities such as *PML::RARA* , *CBFB::MYH11*, and *RUNX1::RUNX1T1*. However, the threshold for patients with *BCR::ABL1* alone was kept at ≥ 20% to avoid confusion with accelerated-phase chronic myeloid leukemia.

(From Reference 3)

One important change in the classification was that two previous entities, acute myeloid leukemia with myelodysplasia-related changes (AML-MRC) and therapy-related myeloid neoplasms, were removed to reflect that genetic characteristics are more relevant than medical history in biological classification of AML.

RARA, *KMT2A*, and *MECOM* were added as entities in the category of AML with recurrent genetic abnormalities. In addition, the biallelic mutated *CEBPA* entity was changed to *CEBPA* bZIP domain mutation because mutations in the bZIP domain are associated with favorable prognosis even in patients with monoallelic mutated *CEBPA*.

TP53-mutated AML became an independent entity, and AML with *ASXL1*, *BCOR*, *EZH2*, *RUNX1*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, or *ZRSR2* mutation became classified as AML with myelodysplasia-related gene mutations, even in the absence of mutated *TP53*, and regardless of whether the patient had a history of MDS. AML without *TP53* or myelodysplasia-related gene mutations was previously classified as AML-MRC, but is now in the newly added category of AML with myelodysplasia-related cytogenetic abnormalities.

Further revisions to disease entities and treatment guidelines are expected as the prognostic impact of various genetic abnormalities and treatment outcomes of newly released drugs are analyzed in detail.

(From Reference 5)

3. Prognostic factors in AML

With standard chemotherapy, the CR rate in younger patients with AML is 70–80% and 5-year relapse-free survival (RFS) rate is approximately 40% overall. Various prognostic factors are used to group patients into three risk groups: favorable risk, intermediate risk, and adverse risk.

The prognosis of AML is related to both patient factors and leukemic cell factors; responsiveness to treatment is also a factor that affects the long-term prognosis (Table 4).[2,6–8]

Important patient factors associated with a poor prognosis are age (≥ 60 years), performance status (≥ 3), and comorbidities (e.g., infection).

Table 3 The 2022 ELN classification of AML

AML with recurrent genetic abnormalities (requiring ≥ 10% blasts in BM or PB)
APL with t(15;17)(q24.1;q21.2)/PML::RARA
AML with t(8;21)(q22;q22.1)/RUNX1::RUNX1T1
AML with inv(16)(p13.1q22)or t(16;16)(p13.1;q22)/CBFB::MYH11
AML with t(9;11)(p21.3;q23.3)/MLLT3::KMT2A
AML with t(6;9)(p22.3;q34.1)/DEK::NUP214
AML with inv(3)(q21.3q26.2)or t(3;3)(q21.3;q26.2)/GATA2, MECOM(EVI1)
AML with other rare recurring translocations
AML with mutated NPM1
AML with in-frame bZIP mutated CEBPA
AML with t(9;22)(q34.1;q11.2)/BCR::ABL1
Provisional entity: AML with mutated RUNX1
Categories designated AML (if ≥ 20% blasts in BM or PB) or MDS/AML (if 10–19% blasts in BM or PB)
AML with mutated TP53
AML with myelodysplasia-related gene mutations
Defined by mutations in ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2
AML with myelodysplasia-related cytogenetic abnormalities
AML not otherwise specified (NOS)
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis associated with Down syndrome
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm
Acute leukemias of ambiguous lineage
Acute undifferentiated leukemia
MPAL with t(9;22)(q34.1;q11.2)/BCR::ABL1
MPAL with t(v;11q23.3)/KMT2A rearranged
MPAL, B/myeloid, not otherwise specified
MPAL, T/myeloid, not otherwise specified

Table 4 Prognostic stratification factors in AML

Stratification factor	Favorable	Unfavorable
Age	≤ 50 years	≥ 60 years
Performance status	≤ 2	≥ 3
Type of onset	De novo	Secondary
Karyotype	t(8;21)(q22;q22.1) inv(16)(p13.1q22) t(16;16)(p13.1;q22) t(15;17)(q24.1;q21.2)	3q abnormalities [inv(3)(q21.3q26.2) t(3;3)(q21.3;q26.2), etc.] Complete deletion of chromosome 5 or chromosome 7 or deletion of the long arm t(6;9) (p23;q34.1) Complex karyotype
Mutations	Mutated *NPM1* Biallelic mutations of *CEBPA*	*FLT3*-ITD mutation
Number of treatment cycles required to achieve remission	1 cycle	≥ 2 cycles

Leukemic cell factors that affect prognosis include karyotype, type of onset (i.e., de novo or secondary), initial white blood cell (WBC) count, and cellular morphology

(presence or absence of dysplasia, FAB subtype, and myeloperoxidase positivity).

Karyotype is the most commonly used factor for prognostic stratification for AML, but it is now known that mutations in various genes are also important prognostic factors, and systems that classify conventional karyotype-based risk into further subcategories by mutation status have been proposed. However, even though fewer mutations have been identified for AML than for solid cancers, combinations of mutations have a concerted effect on the pathology of AML. Consequently, care should be taken in prognostic stratification by individual mutations, and efforts are being made to create stratification systems that consider combinations of multiple mutations. In 2010, ELN proposed a new prognostic stratification system that combined these mutations with conventional karyotype-based prognostic factors. In 2017,[9] and later in 2022,[5] the ELN stratification system was revised to include new cytogenetic abnormalities and mutations (Tables 5, 6). A detailed explanation is provided in CQ1.

(From References 2, 6–8)

(From Reference 9)

(From Reference 5)

Table 6 The 2022 ELN stratification system for AML

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1)/RUNX1::RUNX1T1
	inv(16)(p13.1q22)or t(16;16)(p13.1;q22)/CBFB::MYH11
	Mutated NPM1 without FLT3-ITD
	bZIP in-frame mutated CEBPA
Intermediate	Mutated NPM1 with FLT3-ITD
	Wild-type NPM1 with FLT3-ITD
	t(9;11)(p21.3;q23.3)/MLLT3::KMT2A
	Cytogenetic and/or molecular abnormalities not classified as favorable or adverse
Adverse	t(6;9)(p23;q34.1)/DEK::NUP214
	t(v;11q23.3)/KMT2A-rearranged
	t(9;22)(q34.1;q11.2)/BCR::ABL1
	t(8;16)(p11;p13)/KAT6A::CREBBP
	inv(3)(q21.3q26.2)or t(3;3)(q21.3;q26.2)/GATA2, MECOM (EVI1)
	t(3q26.2;v)/MECOM (EVI1)-rearranged
	− 5 or del(5q); − 7; − 17/abn(17p)
	Complex karyotype, monosomal karyotype
	Mutated ASXL1, BCOR, EZH2, RUNX1, SF3B1, SRSF2, STAG2, U2AF1, or ZRSR2
	Mutated TP53

Table 5 The 2017 ELN stratification system for AML

Risk category	Genetic abnormality
Favorable	t(8;21)(q22;q22.1): RUNX1-RUNX1T1
	inv(16)(p13.1q22)or (t 16;16)(p13.1;q22): CBFB-MYH11
	Mutated NPM1 without FLT3-ITD or with FLT3-ITD low*
	Biallelic mutated CEBPA
Intermediate	Mutated NPM1 and FLT3-ITD high*
	Wild-type NPM1 without FLT3-ITD or with FLT3-ITD low* (without adverse risk genetic lesions)
	t(9;11)(p21.3;q23.3); MLLT-KMT2A[¶]
	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6;9)(q23;q34.1): DEK-NUP214
	t(v;11)(v;q23): KMT2A rearranged
	t(9;22)(q34.1;q11.2); BCR-ABL1
	inv(3)(q21.3q26.2)or (t 3;3)(q21.3;q26.2); GATA2, MECOM (EVI1)
	− 5 or del(5q), − 7, − 17/abn(17p)
	Complex karyotype§, monosomal karyotype[†]
	Wild-type NPM1 and FLT3-ITD high*
	Mutated RUNX1[‡]
	Mutated ASXL1[‡]
	Mutated TP53[#]

[*]Low: low allelic ratio (< 0.5), high: high allelic ratio (≧ 0.5)

[¶]Takes precedence over rare, concurrent adverse-risk gene mutations

[§]Three or more cytogenetic abnormalities, without the following translocations or inversions: t(8;21), inv(16)/t(16;16), t(9;11), t(v;11)(v;q23.3), t(6;9), inv(3)/(t3;3), BCR-ABL1

[†]Defined by the presence of 1 single monosomy (excluding loss of X or Y) in association with at least 1 additional monosomy or structural chromosome abnormality (excluding core-binding factor AML)

[‡]These markers should not be used as an adverse prognostic marker if they co-occur with favorable-risk AML subtypes

[#]*TP53* mutations are significantly associated with AML with complex karyotype

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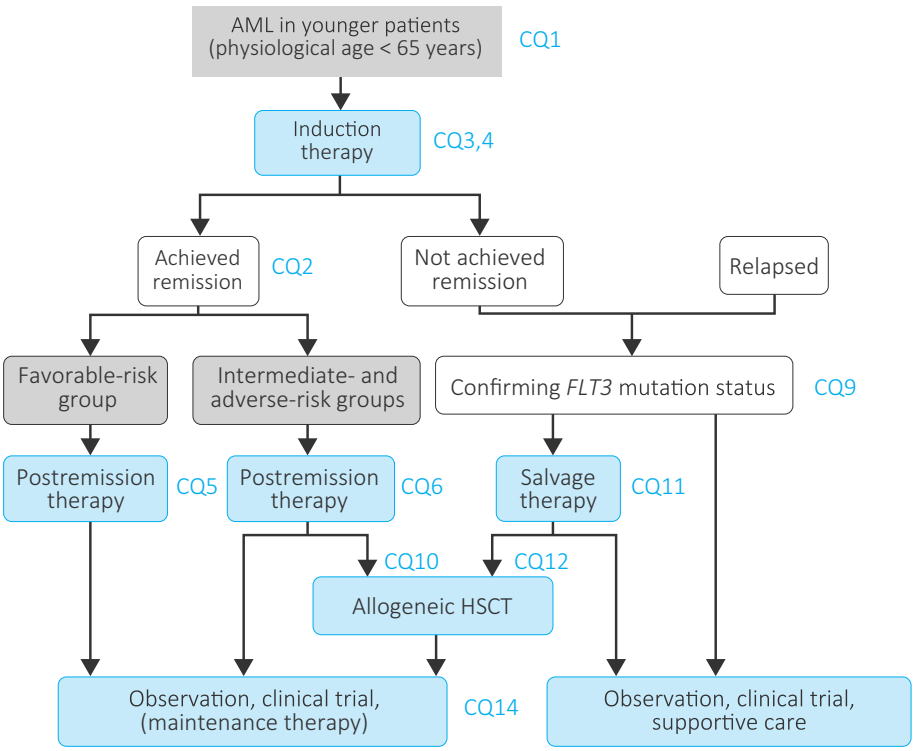
Algorithm



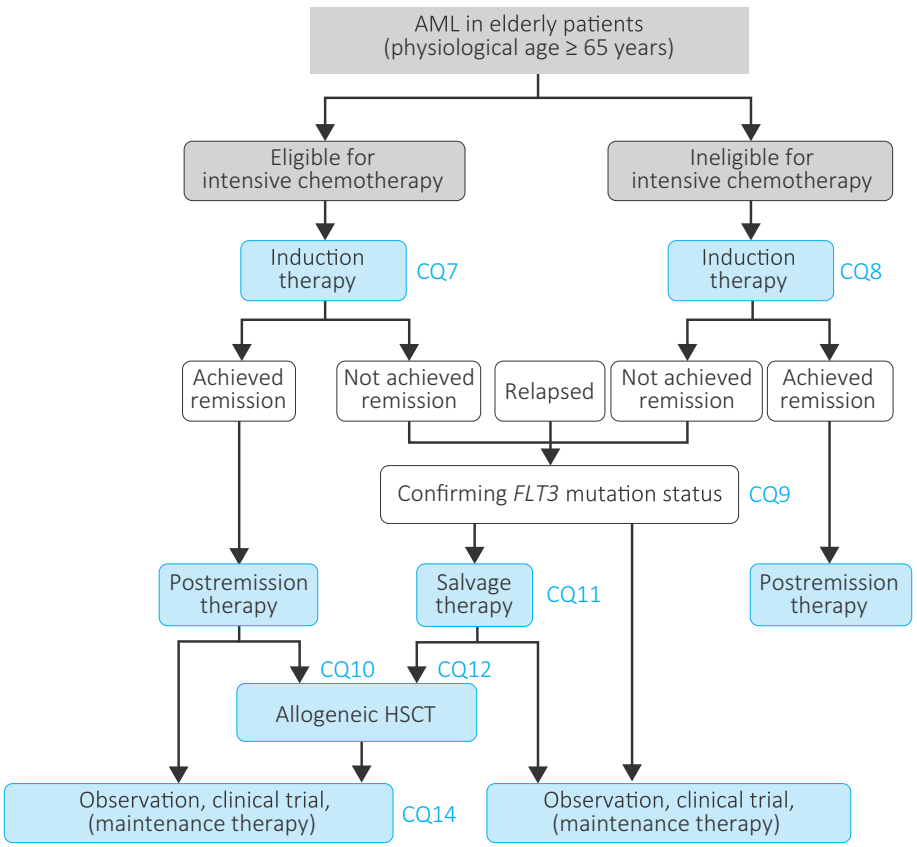
1. AML in younger patients (physiological age < 65 years)

It is recommended to follow the above algorithm after diagnosing AML. The standard induction therapy for AML in younger patients is an anthracycline plus standard-dose cytarabine (CQ3). Although no single anthracycline or dose level is considered to be the optimal choice, use of daunorubicin or idarubicin is recommended. It is common practice to repeat the same regimen when a patient does not achieve remission after the first induction therapy, and it is also reasonable to include high-dose cytarabine in the second induction therapy if it was not included in the first induction therapy (CQ4).

Prognostic classification systems for AML that incorporate mutations as well as karyotype have been proposed (CQ1), and stratification by prognostic factors is performed for consolidation therapy. High-dose cytarabine is recommended for patients in the favorable-risk group (CQ5), whereas allogeneic HSCT is recommended for patients in the intermediate- and adverse-risk groups (CQ10). If a suitable donor is not available, a treatment regimen with a non-cross-resistant anthracycline or three cycles of high-dose cytarabine is recommended (CQ6).

Accurate assessment of minimal/measurable residual disease (MRD) provides useful information for predicting the risk of relapse and creating a personalized treatment strategy, including whether and how to perform HSCT (CQ2).

New evidence suggests that maintenance therapy with an FLT3 inhibitor after allogeneic HSCT for *FLT3*-mutated AML improves prognosis, and this could lead to expanded indications for maintenance therapy depending on future circumstances (CQ14).



2. AML in elderly patients (physiological age ≥ 65 years)

Treatment intensity is determined on the basis of prognostic factors for leukemia, performance status, the wishes of the patient and their family, and the availability of social support such as nursing care. If chemotherapy at the same intensity used for younger patients is possible, cytarabine plus an anthracycline is recommended (CQ7). A standard postremission therapy for elderly patients with AML has not been established, but combination regimens containing a non-cross-resistant anthracycline are commonly used in Japan (CQ7). Non-myeloablative allogeneic HSCT is sometimes performed as postremission therapy for adverse-risk patients. Venetoclax plus azacitidine, venetoclax plus low-dose cytarabine, reduced-intensity therapy, or best supportive care (BSC) should be considered for patients ineligible for intensive chemotherapy (CQ8).

3. Therapy-related and secondary AML

For younger patients (< 65 years) eligible for intensive chemotherapy, it is recommended to achieve remission with chemotherapy, and then perform HSCT when appropriate. For elderly patients and patients ineligible for intensive chemotherapy, venetoclax plus azacitidine should be considered (CQ13).

4. Salvage therapy for relapsed or refractory AML

For younger patients with relapsed or refractory AML, it is recommended to induce CR by high-dose cytarabine-based salvage chemotherapy, then perform HSCT when appropriate (CQ11). For relapsed or refractory *FLT3*-mutated AML, it is recommended to use an FLT3 inhibitor and perform HSCT when appropriate (CQ9).

Options when intensive chemotherapy is not indicated are low-dose cytarabine, gemtuzumab ozogamicin (if $CD33^{+}$), non-intensive chemotherapy such as venetoclax plus azacitidine, and palliative supportive care (CQ11).

5. Allogeneic HSCT for AML not in remission

No specific index for determining eligibility for HSCT has been established for patients not in remission who have not been treated with re-induction therapy for relapsed AML. Moreover, no specific index for determining eligibility for HSCT has been established for patients with AML not in remission due to being refractory to induction therapy (CQ12).

6. Supportive care (G-CSF for neutropenia)

Induction or postremission therapy with granulocyte colony stimulating factor (G-CSF) for AML can shorten the duration of neutropenia and improve quality of life during this phase. It may be considered for elderly patients and patients with severe concomitant infections (CQ15).

CQ1 Is genetic testing useful for treatment selection and prognostic stratification in AML?

Recommendation grade: Category 2A

Karyotyping is essential for prognostic stratification and treatment selection, including determination of transplant eligibility. Analysis of mutations in genes such as *FLT3*, *NPM1*, *CEBPA*, and *TP53* enables further prognostic stratification.

Explanation

AML cell karyotype is a strong predictor of response to induction therapy and of survival, and is important information for subtyping by the 2017 WHO classification and for treatment selection.

Younger patients are classified by karyotype and associated chimeric genes into three groups: favorable risk, intermediate risk, and adverse risk.[1] In the 2022 National Comprehensive Cancer Network (NCCN) Guidelines (Ver. 1), t(8;21) (q22;q22.1)/*RUNX1::RUNX1T1*, inv(16) (p13.1q22) or t(16;16) (p13.1;q22)/*CBFB::MYH11* are considered favorable-risk karyotypes, inv(3) (q21.3q26.2) or t(3;3) (q21.3;q26.2), -5 or del(5q), and -7, -17, or 17p abnormalities, t(6;9) (p23;q34.1)/*DEK::NUP214*, translocations involving *KMT2A* (*MLL*) (11q23) other than t(9;11)

(p21.3;q23.3), t(9;22) (q34.1;q11.2)/*BCR::ABL1*, complex karyotypes, and monosomal karyotype are considered adverse-risk karyotypes, and normal karyotype, t(9;11)(p21.3;q23.3)/*MLLT3::KMT2A*, and all other karyotypes are classified as intermediate-risk karyotypes.[2]

The ELN recommendations have also included a prognostic classification system since 2017.[3] They note that in addition to following the conventional karyotype-based risk classification system, it is important to assess the *FLT3*-ITD allelic ratio and *NPM1* mutation status, biallelic mutated *CEBPA*, and *ASXL1*, *RUNX1*, and *TP53* mutation status in patients with an intermediate-risk karyotype.[4] A large body of validating data has been generated from studies conducted to establish the usefulness of the 2017 ELN recommendations,[5] and major treatment guidelines including those of the NCCN now recommend treatment selection based on the 2017 ELN recommendations. The NCCN guidelines classify mutated *NPM1* without *FLT3*-ITD or with low allelic ratio *FLT3*-ITD (< 0.5) as favorable risk, mutated *NPM1* with high allelic ratio *FLT3*-ITD (> 0.5) and unmutated *NPM1* without *FLT3*-ITD or with low allelic ratio *FLT3*-ITD as intermediate risk, and unmutated *NPM1* with high allelic ratio *FLT3*-ITD as adverse risk. In addition, they classify biallelic mutated *CEBPA* as favorable risk and *RUNX1*, *ASXL1*, and *TP53* mutations as adverse risk.

When the ELN guidelines were revised in 2022, the prognostic factors for AML were also changed (see Table 6 in Overview section).[6]

Important changes include the following:

(1) The *FLT3*-ITD allelic ratio was no longer considered in risk classification; instead, all patients with *FLT3*-ITD were classified as intermediate risk, regardless of allelic ratio or *NPM1* mutation status (if eligible for FLT3 inhibitors at the time of initial treatment).
(2) AML with myelodysplasia-related gene mutations was classified as adverse risk, and the mutations in this category now include not only *ASXL1* and *RUNX1* but also *BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2*.
(3) All *CEBPA* bZIP domain mutations, whether monoallelic or biallelic, were classified as favorable risk.
(4) Mutations added to the category of AML with recurrent genetic abnormalities, including *MECOM* and *KAT6A::CREBBP* fusion gene, were classified as adverse risk.

If global gene mutation analysis becomes available in Japan in the future, it will hopefully be leveraged in treatment selection in routine practice, for example, to use molecularly targeted agents starting from initial therapy, to determine the indication for HSCT in first remission, and as a marker of MRD.

(Note: In May 2023, the FLT3 inhibitor quizartinib was approved for previously untreated *FLT3*-ITD AML in Japan.)

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CQ2 Is MRD assessment useful for risk stratification and treatment selection for AML?

Recommendation grade: Category 2A
Options to consider for monitoring measurable residual disease in AML over time include quantification of mRNA expression of disease-specific chimeric genes or *WT1*.

Explanation

Accurate assessment of MRD provides useful information for predicting the risk of relapse and creating a personalized treatment strategy, including whether and how to perform HSCT. Methods for MRD assessment include quantification of disease-specific gene expression by RQ-PCR, analysis of specific cell surface markers by multi-parameter flow cytometry (MFC), and gene mutation analysis by next-generation sequencing methods currently under development.[1,2] The ELN MRD Working Party recommendations on use of MRD in AML treatment emphasize the importance of understanding the characteristics and sensitivity of each technique for MRD assessment, continuously monitoring MRD over the course of treatment, and appropriately interpreting MRD results obtained at each time point with consideration to the nature of the treatment.

In core-binding factor (CBF) leukemia with *RUNX1::RUNX1T1* and *CBFB::MYH11*, RQ-PCR targeting chimeric genes is highly sensitive and disease specific, and the correlation between MRD and prognosis has been investigated extensively. Patients with a greater than 3-log decrease in MRD based on chimeric gene expression levels from initial diagnosis or undetectable MRD after induction therapy or consolidation therapy have a significantly lower relapse rate, and this characteristic is considered to predict a favorable survival rate.[3–6] The 2022 NCCN Guidelines (Ver. 1) recommend consolidation therapy for MRD-negative patients and allogeneic HSCT for MRD-positive patients as postremission therapy for CBF leukemia. Evidence has been reported that quantitative MRD by RQ-PCR for *NPM1* mutations is a prognostic factor,[7] but only approximately 20% of patients with AML have this mutation, and it has been only analyzed for research purposes due to the great variety in mutation sites. Quantification of *WT1* in peripheral blood, which is widely performed in Japan, is not specific for AML, but is recommended for MRD assessment when no other appropriate targets are available for MRD testing,[8,9] because *WT1* MRD results shortly after induction of remission are correlated with prognosis.[1]

MFC, which is the most popular method for AML MRD assessment in Europe and the United States, is not covered by Japanese National Health insurance. A panel combining several antigens, such as different from normal (DfN) and leukemia-associated immunophenotype (LAIP), must be used to identify MRD markers in individual patients.[1,2] Methods for MRD analysis by next-generation sequencing are also under development, but some issues must be resolved, such as the fact that persistence of frequently observed mutations involved in clonal hematopoiesis (*DNMT3A*, *TET2, ASXL1*) does not correlate with prognosis, which mutations to target, and measurement sensitivity.[10]

The above results indicate that quantification of mRNA expression of disease-specific chimeric genes or *WT1* should be considered as options for assessment of MRD over time. However, other MRD tests have not yet been standardized in Japan.

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CQ3 What induction therapy regimens are recommended for younger patients (< 65 years) with newly diagnosed AML?

Recommendation grade: Category 1 The standard induction therapy regimen for younger patients with *de novo* AML is an anthracycline (idarubicin or daunorubicin) plus standard-dose cytarabine.

Explanation

The standard induction therapy regimen for de novo AML in younger patients (< 60 years) used to be the "3 + 7" regimen consisting of 45–50 mg/m^2 of daunorubicin for 3 days plus continuous infusion of 100 or 200 mg/m^2 of cytarabine for 7 days. However, comparative studies and meta-analysis of idarubicin plus cytarabine and daunorubicin plus cytarabine demonstrated the superiority of idarubicin plus cytarabine.[1] Nevertheless, the conventional dose of daunorubicin (45–50 mg/m^2) was found to be biologically lower than the dose of idarubicin (12 mg/m^2).

The Eastern Cooperative Oncology Group in the United States conducted a randomized controlled trial (RCT) comparing higher dose daunorubicin (90 mg/m^2) for 3 days plus cytarabine (100 mg/m^2) for 7 days with the conventional regimen of daunorubicin (45 mg/m^2) for 3 days plus cytarabine (100 mg/m^2) for 7 days in patients younger than 60 years with de novo AML, and found that remission and survival rates were significantly higher in the high-dose daunorubicin (90 mg/m^2) group.[2]

The British National Cancer Research Institute conducted a trial comparing daunorubicin doses of 90 mg/m^2 or 60 mg/m^2 for 3 days and found no significant difference in remission and survival rates, but a significantly higher mortality rate with daunorubicin 90 mg/m^2 at Day 60.[3]

An RCT (AML201 study) by the Japan Adult Leukemia Study Group (JALSG) comparing daunorubicin (50 mg/m^2) for 5 days plus cytarabine against idarubicin (12 mg/m^2) for 3 days plus cytarabine showed that remission and survival rates were comparable between regimens.[4]

Another anthracycline that has been investigated is mitoxantrone (total dose 18–30 mg/m^2), which showed no significant difference in remission and survival rates compared with idarubicin (total dose 24–36 mg/m^2) in an RCT.[5]

Therefore, the standard induction therapy regimen for younger patients with de novo AML is idarubicin plus cytarabine or daunorubicin plus cytarabine. The NCCN guidelines recommend that a daunorubicin dose of 60–90 mg/m^2 for 3 days be used when combining daunorubicin with cytarabine,[6] but comparable outcomes have been observed at a dose of 50 mg/m^2 for 5 days. It is also necessary to be aware that the approved dosage of daunorubicin in Japan is 3–5 doses of 1 mg per kg body weight administered daily or on alternating days.

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CQ4 What therapy is recommended for newly diagnosed AML after failure to achieve CR with the first induction therapy?

Recommendation grade: Category 2B It is reasonable to repeat the same regimen used for the first induction therapy.
Recommendation grade: Category 3 If the first induction therapy did not include high-dose cytarabine, a second induction therapy that includes high-dose cytarabine may improve the remission rate for some patients.

Explanation

The JALSG has conducted many studies on treatment of newly diagnosed AML in Japan. In past JALSG studies, when CR was not achieved after the first induction therapy, the same regimen used in the first induction therapy was repeated as the second induction therapy.[1–6] In the AML201 study, 78.2% of the idarubicin plus cytarabine group (IDR group) and 77.5% of the daunorubicin plus cytarabine group (DNR group) achieved CR, and among those, 64.1% in the IDR group and 61.1% in the DNR group achieved remission after the first induction therapy, and 14.1% in the IDR group and 16.4% in the DNR group required the second induction therapy.[6] This means that the estimated remission rate when patients who did not achieve remission after the first induction therapy undergo the second induction therapy with the same regimen would be a relatively high 40% in the IDR group and 42% in the DNR group. In addition, a retrospective analysis by Othus et al. showed that the remission rate when patients resistant to the first induction therapy underwent the second induction therapy with the same regimen was 43%, and subsequent survival was similar regardless of whether patients underwent the second induction therapy with the same regimen or alternative therapies.[7]

Another option besides repeating the same regimen used for the first induction therapy may be switching to a regimen including high-dose cytarabine, which has been shown to be effective for relapsed or refractory AML. However, no study has clearly demonstrated the superiority of this approach. Ravandi et al. reported that 18% of patients not in remission after the first induction therapy containing high-dose cytarabine achieved remission after the second induction therapy.[8] This suggests that using an intensive regimen for the first induction therapy may reduce the effect of the second induction therapy. Another study reported results of the treatment strategy where the second induction therapy is performed regardless of response to the first induction therapy.[9] In that study, patients aged 60 years or younger either received standard-dose cytarabine for both the first and second induction therapies (TAD-TAD group) or standard-dose cytarabine for the first and high-dose cytarabine for the second (TAD-HAM group), but the remission rate did not differ significantly between groups (65% for TAD-TAD vs. 71% for TAD-HAM, $p = 0.072$). Subgroup analysis showed that TAD-HAM was significantly superior to TAD-TAD for patients with pretreatment LDH > 700 IU/L, adverse-risk cytogenetics, or myeloblasts > 40% on day 16 after induction therapy, with a remission rate of 65 versus 49% ($p = 0.004$). However, the CR rate did not differ significantly between TAD-HAM and TAD-TAD in the population of patients without the above factors.

In conclusion, if remission is not achieved after the first induction therapy, it is reasonable to repeat the same regimen for the second induction therapy because this approach has been used in several clinical studies and can be expected to yield a relatively high remission rate. However, switching to a different regimen, such as one with high-dose cytarabine, may improve remission rates in some patients. The induction therapy strategy used outside of Japan is combination therapy with either an FLT3 inhibitor or gemtuzumab ozogamicin, depending on the AML classification. These combination therapies can also be considered for the second induction therapy, but are not currently covered by Japanese National Health Insurance. Future drug approvals may also lead to changes in regimen selection for the second induction therapy.

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CQ5 What postremission therapy is recommended for newly diagnosed CBF-AML in younger patients (< 65 years)?

Recommendation grade: Category 2A
High-dose cytarabine is recommended as postremission therapy for patients younger than 65 years with CBF-AML as it has been shown to prolong disease-free survival (DFS) in this group.

Explanation

Cancer and Leukemia Group B (CALGB) conducted a prospective RCT comparing normal-dose cytarabine (100 mg/m^2/day by continuous infusion for 5 days), intermediate-dose cytarabine (400 mg/m^2/day by continuous infusion for 5 days), and high-dose cytarabine (3 g/m^2 twice daily by 3-h infusion on days 1, 3, and 5) as postremission therapy for AML. They found that high-dose cytarabine was effective in patients aged 60 years and younger.[1] High-dose cytarabine has been shown to be the most effective option for CBF leukemia,[2] and another retrospective analysis by CALGB showed that three or more cycles of high-dose cytarabine are also effective against t(8;21) AML.[3] Although inv(16)/t(16;16) does not affect OS because AML patients with it respond well to post-relapse salvage therapy by HSCT, those who receive three to four cycles of high-dose cytarabine have a significantly lower relapse rate than those who receive only one cycle. A prospective study conducted in Japan comparing high-dose cytarabine (twice daily 3-h infusions of 2 g/m^2 for 5 days) with conventional combination therapy in patients under 65 years found no difference in DFS or OS but did find a trend toward improvement in DFS with high-dose cytarabine in CBF leukemia.[4]

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CQ6 What postremission therapy regimens are recommended for younger patients (< 65 years) with newly diagnosed AML other than CBF-AML?

Recommendation grade: Category 2B Four cycles of combination chemotherapy using a non-cross-resistant anthracycline is recommended.
Recommendation grade: Category 3 Three cycles of high-dose cytarabine is recommended. However, caution must be taken as studies have shown that incidence of infection is higher than that with combination chemotherapy.

Explanation

AML requires postremission therapy to maintain durable remission after induction therapy. Cytarabine has long been used for postremission therapy in Europe and the United States, and the effect of cytarabine dosage on treatment outcomes is well investigated. Mayer et al. found that high-dose cytarabine (3 g/m^2, twice daily on days 1, 3, 5 doses, 4 cycles) was superior to standard-dose cytarabine (100 mg/m^2, 400 mg/m^2) in DFS in patients aged 60 years and younger.[1] Subsequent studies on optimal cytarabine dosage showed that even a reduced dose of 1–1.5 g/m^2 produced equivalent treatment outcomes to a dose of 3 g/m^2, and cytarabine dose reduction reduced transfusion volume and shortened the duration of neutropenia.[2,3]

Studies have also compared combination therapy including standard-dose cytarabine against high-dose cytarabine alone.[4,5] JALSG conducted an RCT comparing high-dose cytarabine (2 g/m^2 twice daily for 5 days) against combination therapy consisting of standard-dose cytarabine plus a non-cross-resistant anthracycline.[5] Five-year DFS rate did not differ significantly between high-dose cytarabine and combination therapy (43% vs. 39%) and OS was also similar. No difference in non-relapse mortality (NRM) was observed, but Grade 3 and 4 clinical infections were significantly more common with high-dose cytarabine than combination therapy (20.9 vs. 14.5%).[5,6] Stratified analysis showed a trend toward better DFS with high-dose cytarabine in patients with favorable-risk cytogenetics, but no difference among patients with intermediate- or adverse-risk cytogenetics.

Recent studies have reported the usefulness of combination with gemtuzumab ozogamicin or FLT3 inhibitors in postremission therapy.[7,8] However, these drugs have not been approved for newly diagnosed AML in Japan. The efficacy of autologous peripheral blood stem cell transplantation (PBSCT) has also been investigated; Vellenga et al. compared intensive consolidation therapy with autologous PBSCT for AML in first remission and found that DFS was improved with autologous PBSCT but OS was similar.[9]

Based on the above findings, postremission therapy with four cycles of combination chemotherapy using a non-cross-resistant anthracycline is recommended for newly diagnosed AML other than CBF-AML in younger patients. Three cycles of high-dose cytarabine should be equally effective, but caution must be taken for infection as high-dose cytarabine causes more severe leukopenia than combination chemotherapy. Depending on which drugs are approved in Japan in the future, introduction of molecularly targeted agents will very likely lead to stratification of postremission therapy. Combination therapy with the FLT3 inhibitor quizartinib was shown to be effective in previously untreated *FLT3*-ITD AML,[10] and became covered by Japanese National Health Insurance in May 2023. Therefore, high-dose cytarabine plus quizartinib is recommended as postremission therapy for previously untreated *FLT3*-ITD AML.

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CQ7 What treatment is recommended for elderly patients (≥ 65 years) with AML who are eligible for intensive chemotherapy?

Recommendation grade: Category 2A Intensive chemotherapy with cytarabine plus an anthracycline is recommended for patients classified as favorable- or intermediate-risk per the 2022 ELN recommendations who have good performance status and adequate organ function.

Explanation

There are three main approaches to treatment of AML in elderly patients: intensive chemotherapy similar to that used in younger patients, non-intensive chemotherapy, and palliative supportive care. Treatment is selected on the basis of four factors: prognostic factors for leukemia, performance status and cognitive function, the wishes of the patient and their family, and the availability of social support such as nursing care. Even in elderly patients, intensive induction therapy improves the remission rate and extends survival.[1] The 2022 ELN recommendations use cytogenetic abnormalities and mutations to stratify patients with AML into three prognostic risk groups.[2] Elderly patients are more likely to be in the adverse-risk group, which has a lower CR rate and OS with intensive chemotherapy.[3–5] Although chronologic age is insufficient information to evaluate performance status in elderly patients, the CR rate and OS after intensive chemotherapy generally decrease with age.[3,5] In addition, patients older than 75 years and patients with performance status of 3 or 4 have an increased risk of early death from induction therapy.[5] Eligibility criteria for the Japanese JALSG-GML200 study of AML in elderly patients were adequate hepatic (serum bilirubin < 2.0 mg/dL), renal (serum creatinine < 2.0 mg/dL), cardiac (left ventricular ejection fraction > 50%), and pulmonary functions and performance status of 0–2.[6] Based on the above, the general guidance is that patients in the favorable- or intermediate-risk group per the 2022 ELN recommendations who have good performance status and adequate organ function, and are no older than 75 years should be considered candidates for intensive chemotherapy. Performance status should generally be 0–2, and eligibility of PS 2 patients should be determined comprehensively based on factors such as organ function and comorbidities.

The key agents are cytarabine and anthracyclines. Research has shown no difference in CR rate or DFS between anthracyclines in induction therapy.[4] Increasing the dose of daunorubicin (90 mg/m^2 for 3 days) provides no benefit in patients aged 65 years and older.[3] In addition, increasing the dose of cytarabine does not improve the therapeutic effect in elderly patients. Based on the above, the guidance is to select standard-dose cytarabine plus an anthracycline for intensive induction therapy in elderly patients with AML.

Various consolidation therapies including intermediate-dose cytarabine, combination including mitoxantrone, and reduced-dose anthracycline have been investigated, but a standard consolidation therapy for elderly patients with AML has not been established.[7–9]

In Japan, the JALSG-GML200 study compared daunorubicin (on a fixed schedule of 40 mg/m^2 for 3 days) plus the cytarabine derivative enocitabine (on a fixed schedule of 200 mg/m^2 for 8 days) against daunorubicin (40 mg/m^2 for ≥ 3 days) plus enocitabine (200 mg/m^2 for ≥ 8 days) (with additional agents as needed based on myeloblast reduction) as induction therapy for elderly patients with AML (65–79 years) (however, the daunorubicin dose for patients ≥ 70 years was 30 mg/m^2).[6] The average total drug doses were 109 mg/m^2 daunorubicin and 1605 mg/m^2 enocitabine for the fixed schedule and 139 mg/m^2 daunorubicin and 1851 mg/m^2 enocitabine for the incremental schedule. The CR rate was 60.1% for the fixed schedule and 63.6% for the incremental schedule. Patients then received three cycles of consolidation therapy with enocitabine. Estimated 4-year RFS was 9% for the fixed schedule and 18% for the incremental schedule. This approach is an option for intensive chemotherapy. Standard-dose cytarabine can be substituted for enocitabine.

The AZA-AML-001 trial, which compared azacitidine with conventional treatments (standard induction chemotherapy, low-dose cytarabine, and supportive care only) in elderly patients with newly diagnosed AML not eligible for HSCT (≥ 65 years, excluding favorable-risk patients), showed no difference in OS.[10] Azacitidine was effective in subgroups such as patients with adverse-risk cytogenetics and AML-MRC. Further investigation of the clinical efficacy of novel agents such as azacitidine and venetoclax in elderly patients eligible for intensive chemotherapy is warranted.[11]

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CQ8 What treatment is recommended for elderly patients (≥ 65 years) with AML who are ineligible for intensive chemotherapy?

Recommendation grade: Category 1

Venetoclax plus azacitidine or venetoclax plus low-dose cytarabine is recommended for elderly patients with AML who are not eligible for intensive chemotherapy. However, it may be necessary to consider reduced-intensity treatment or BSC in elderly patients with AML depending on performance status or severity of comorbidities.

Explanation

Until recently, treatment for unfit elderly patients with AML considered ineligible for standard chemotherapy consisted of reduced-intensity combination chemotherapy, single-agent therapy with low-dose cytarabine or with azacitidine,[1,2] or the CAG (low-dose cytarabine, aclarubicin, and G-CSF) regimen, determined by the treating physician depending on the patient's organ function and comorbidities. As there was no evidence to establish criteria for reducing treatment intensity and no guidelines regarding treatment frameworks such as what consolidation therapy should follow induction therapy, treating physicians made their own decisions regarding continuation, modification, and discontinuation of their selected treatment depending on response. There was previously no consensus on a recommended standard regimen for AML in unfit elderly patients.

In 2020, clinical trials of the BCL2 inhibitor venetoclax demonstrated the efficacy of venetoclax plus azacitidine (VIALE-A trial)[3] and venetoclax plus low-dose cytarabine[4] in patients with newly diagnosed AML who were either 75 years or older, or under 75 years but judged as unfit. Criteria for unfit patients in these trials included performance status of 2 or 3, chronic heart failure requiring treatment, ejection fraction ≤ 50%, history of chronic stable angina, $DL_{CO} \leq 50\%$, FEV1 ≤ 65%, $C_{Cr} \geq 30$ mL/min to < 45 mL/min, and moderate hepatic dysfunction with total bilirubin ≥ 1.5 times to ≤ 3 times the upper limit of the institutional reference range. In the VIALE-A trial, 431 patients with a median age of 76 years (49–91 years) were randomized to receive venetoclax plus azacitidine or azacitidine alone, and median survival (14.7 months for venetoclax + azacitidine vs. 9.6 months for azacitidine alone; HR 0.66, 95% CI 0.52–0.85, $p < 0.001$), CR rate (36.7 vs. 17.9%, $p < 0.001$), and CR + CRi rate (66.4 vs. 28.3%, $p < 0.001$) were all better for venetoclax plus azacitidine. In analysis by mutation group, venetoclax plus azacitidine yielded a higher composite remission rate for *IDH1/2* (75.4 vs. 10.7%, $p < 0.001$), *FLT3* (72.4 vs. 36.4%, $p = 0.021$), *NPM1* (66.7 vs. 23.5%), and *TP53* (55.3 vs. 0%) mutations. Subgroup analysis showed that venetoclax plus azacitidine improved survival rates in de novo AML (HR 0.67, 95% CI 0.51–0.90), secondary AML (HR 0.56, 95% CI 0.35–0.91), AML-MRC with myelodysplasia-related changes (HR 0.73, 95% CI 0.48–1.11), AML with intermediate-risk cytogenetics (HR 0.57, 95% CI 0.41–0.79), and AML with adverse-risk cytogenetics (HR 0.78, 95% CI 0.54–1.12). The adverse event of Grade 3 or higher febrile neutropenia was more frequent with venetoclax plus azacitidine (42 vs. 19%). Physicians must familiarize themselves with management strategies for venetoclax plus azacitidine therapy, including its hematologic toxicity and interactions with concomitant medications such as azole antifungals. No effective treatment options were available for unfit elderly patients with AML until venetoclax plus azacitidine was demonstrated effective.[5] However, some issues with the venetoclax plus azacitidine regimen remain to be resolved, including response durability, maintenance therapy after remission, and subsequent treatment for relapsed or refractory disease to this regimen. As molecularly targeted agents for patients with actionable mutations (*IDH1/2* and *FLT3*) are expected to become available in Japan in the future as well, further research will be needed to determine how to combine these agents with venetoclax plus azacitidine.[6]

Lower intensity therapy or BSC should be considered for patients with serious comorbidities and unfit elderly AML patients with performance status of 3 or higher if these patients are considered to have a higher risk of treatment-related mortality from venetoclax-based therapy.

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CQ9 What treatments are recommended for *FLT3*-mutated AML? Also, what are important points to note when using the LeukoStrat CDx *FLT3* Mutation Assay?

Recommendation grade: Category 2A

For younger patients with newly diagnosed *FLT3*-ITD AML, it is recommended to induce CR by chemotherapy, then perform HSCT when appropriate. Azacitidine plus venetoclax is an option for patients with newly diagnosed AML who are ineligible for intensive chemotherapy. For relapsed or refractory AML, it is recommended to use an FLT3 inhibitor and perform HSCT when appropriate. When using an FLT3 inhibitor, *FLT3*-ITD or *FLT3*-TKD positivity must be confirmed by the LeukoStrat CDx *FLT3*Mutation Assay.

Explanation

FLT3 mutations are the most common mutations in AML,[1] detected in approximately 25% of newly diagnosed AML cases in Japan.[2] There are two types: internal tandem duplication (ITD) in part of the transmembrane domain and missense mutation in the tyrosine kinase domain (TKD). *FLT3*-ITD is associated with a poor prognosis;[3] patients with this mutation have a higher relapse rate as well as shortened duration of remission and OS.[4–8] In contrast, *FLT3*-TKD has not been established as an unfavorable prognostic factor.

The RATIFY trial investigated combination chemotherapy with the FLT3 inhibitor midostaurin in younger patients with newly diagnosed *FLT3*-ITD or *FLT3*-TKD positive AML. The CR rate was 58.9% for combination therapy with midostaurin versus 53.5% for therapy without midostaurin ($p=0.15$), and median OS was 74.7 versus 25.6 months ($p=0.009$).[9] However, the fact that midostaurin is not approved in Japan must be considered in treatment strategy planning. In the JALSG-AML209-FLT3-SCT study, which prospectively investigated allogeneic HSCT in first remission in younger patients with newly diagnosed *FLT3*-ITD AML, the 3-year DFS rate was 43.8%.[10] Oran et al. found that allogeneic HSCT in first remission yielded better RFS and OS than chemotherapy for *FLT3*-ITD AML.[11] Based on this evidence, the recommendation for younger patients with newly diagnosed *FLT3*-ITD AML is to induce CR by chemotherapy, then perform allogeneic HSCT when appropriate. A Japanese retrospective analysis showed that allogeneic HSCT in first remission improved RFS and OS in patients with *NPM1* mutation and low allelic ratio *FLT3*-ITD, which were classified as favorable risk in the 2017 ELN recommendations.[12,13] The 2022 ELN recommendations classify *FLT3*-ITD as intermediate risk regardless of allelic ratio or *NPM1* mutation status.[14] However, this assumes that midostaurin combination therapy will be performed. In May 2023, combination chemotherapy for previously untreated *FLT3*-ITD AML was added to the approved indications for quizartinib, making it a new treatment option.[15].

No established treatment exists for patients with newly diagnosed *FLT3*-ITD AML who are ineligible for intensive chemotherapy. A subgroup analysis of the phase III VIALE-A trial of azacitidine plus venetoclax showed a remission rate (CR + CRi) of 72.4% and median OS of 13.6 months in patients with *FLT3*-mutated AML (including both *FLT3*-ITD and *FLT3*-TKD).[16,17] Venetoclax combination therapy is an option for this patient group. It should be noted that median OS was 9.9 months with combination therapy versus 8.5 months with azacitidine alone for *FLT3*-ITD, and a respective 19.2 and 10.0 months for *FLT3*-TKD.[17]

The prognosis for relapsed or refractory *FLT3*-ITD AML is very poor. In a retrospective analysis by Ravandi et al., the remission rate for relapsed AML treated with chemotherapy was 24% for patients positive for the *FLT3*-ITD mutation versus 38% for those negative for the mutation ($p=0.09$).[18] In Japan, the FLT3 inhibitors gilteritinib and quizartinib are covered by National Health Insurance for relapsed or refractory disease. Gilteritinib is eligible for both

FLT3-ITD and *FLT3*-TKD, while quizartinib is only eligible for *FLT3*-ITD. As mutation status can change between initial onset and recurrence, *FLT3*-ITD or *FLT3*-TKD positivity must be confirmed by the LeukoStrat CDx *FLT3* Mutation Assay before using an FLT3 inhibitor.[19] The ADMIRAL trial compared gilteritinib against salvage chemotherapy in patients with relapsed or refractory *FLT3*-ITD and *FLT3*-TKD AML.[20] Median OS was 9.3 months with gilteritinib versus 5.6 months with salvage chemotherapy, and the composite CR rate (CR + CRp + CRi) was 54.3% with gilteritinib versus 21.8% with salvage chemotherapy. A subgroup analysis in Japanese patients showed similar results.[21] The QuANTUM-R trial compared quizartinib against salvage therapy in patients with relapsed or refractory *FLT3*-ITD AML.[22] Median OS was 6.2 months with quizartinib versus 4.7 months with salvage therapy, and the composite CR rate was 48.2% with quizartinib versus 27.0% with salvage therapy. In both trials, treatment with an FLT3 inhibitor increased the percentage of patients who underwent HSCT.

Based on the above, the recommendation for patients with relapsed or refractory disease is to use an FLT3 inhibitor and perform HSCT when appropriate. It should be noted that in the ADMIRAL trial, median OS in the *FLT3*-TKD subgroup tended to be better with gilteritinib than salvage chemotherapy (8.0 vs. 5.7 months).

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CQ10 What are the eligibility criteria for allogeneic HSCT in AML patients in first remission?

Recommendation grade: Category 1

At present, prognostic stratification by karyotype and genetic abnormalities present at diagnosis is important. HSCT in first remission is recommended for patients classified in the intermediate- and adverse-risk groups.

Explanation

Many RCTs have compared allogeneic HSCT and postremission chemotherapy for AML in first remission and show that allogeneic HSCT extends DFS in many patients. However, most studies have failed to demonstrate OS benefit. A meta-analysis of 24 clinical studies (3638 patients) conducted as a secondary study to supplement these findings found that HSCT significantly improved the survival rate in AML patients in first remission with adverse-risk and intermediate-risk cytogenetic abnormalities, but not in patients with favorable-risk cytogenetic abnormalities.[1] Based on these results, consideration of the presence and type of cytogenetic abnormalities is a reasonable approach to judging eligibility for HSCT in AML patients in first remission.

Most RCTs have used HLA-matched related donors, but studies have shown that outcomes of HSCT from an HLA allele-matched unrelated donor are nearly comparable to those of HSCT from an HLA-matched related donor.[2,3] A meta-analysis of nine clinical studies (2258 patients) showed that HLA-haploidentical transplantation with post-transplantation cyclophosphamide had almost identical outcomes to HLA-matched transplantation.[4]

AML with normal karyotype is considered intermediate risk in the karyotype-based classification, but recent accumulation of evidence on the prognostic impact of mutations prompted ELN to publish a new expert consensus in 2022 as the follow-up to their 2017 consensus. Between the 2017 version[5] and the 2022 version[6] of the ELN recommendations, two myelodysplasia-related gene mutations (*MECOM* and *KAT6A::CREBBP* fusion gene) and several recurrent genetic abnormalities (*BCOR*, *EZH2*, *SF3B1*, *SRSF2*, *STAG2*, *U2AF1*, and *ZRSR2* mutations) were added to the adverse-risk group, and are now considered as indications for HSCT during first remission (see CQ1).

RUNX1::RUNX1T1 and *CBFB::MYH11* fusion genes and *CEBPA* bZIP domain mutation are classified as favorable risk and are not indications for HSCT during first remission. Patients with *NPM1* mutation and without *FLT3*-ITD are also classified in the favorable-risk group, and although some studies have shown that transplantation significantly improves RFS in this group,[7] HSCT during first remission is not indicated because a subgroup analysis of previous large RCTs showed that HSCT using an HLA-matched related donor did not improve prognosis.[8] While the 2017 ELN recommendations classified patients with low allelic ratio *FLT3*-ITD (<0.5) and *NPM1* mutation as favorable risk, the 2022 recommendations classified all patients with *FLT3*-ITD as intermediate risk regardless of allelic ratio or *NPM1* mutation status. A retrospective study from Japan showed that HSCT in first remission improved RFS and OS in patients with *NPM1* mutation and low allelic ratio *FLT3*-ITD.[9] There is no consensus regarding the indication for HSCT during first remission in patients with *NPM1* mutation and low allelic ratio *FLT3*-ITD, and future availability of FLT3 inhibitors may change the situation.[10] It is also anticipated that MRD assessment will be used to determine eligibility for HSCT.

In transplant medicine, HSCT is selected with consideration to not only disease risk based on karyotype and mutations but also HSCT-related toxicity. Therefore, firm evidence has not been established because the diversity of

patient characteristics complicates patient matching. Bone marrow banks and regional core hospitals for HSCT in Japan are currently gathering data from more patients, and analysis of that data is awaited.

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CQ11 What treatments are recommended as salvage therapy for relapsed or refractory AML?

Recommendation grade: Category 2A

For younger patients with relapsed or refractory AML, it is recommended to induce CR by high-dose cytarabine-based salvage chemotherapy, then perform HSCT when appropriate. Non-intensive chemotherapy or palliative supportive care is the options for patients not eligible for intensive chemotherapy.

Explanation

Kurosawa et al. found that 50% of patients with relapsed AML (median age 53 years, 16–70 years) achieved a second CR with chemotherapy, with remission rates of 84% for patients with inv(16)(p13.1q22), 58% for those with t(8;21)(q22;q22), 48% for intermediate-risk patients, and 31% for adverse-risk patients.[1] In the intermediate- and adverse-risk groups, patients who underwent HSCT in second remission had superior OS compared with those who did not. In a study by Sarkozy et al., two-thirds of elderly patients with AML in first relapse (median age 64 years, 50–80 years) received re-induction therapy. The CR rate was 31%, and median survival after relapse was 17.3 months in patients who achieved second remission versus 4.2 months in those who did not.[2] These findings indicate that the best strategy for relapsed or refractory AML is to induce CR by chemotherapy, then perform HSCT when appropriate.

Many salvage chemotherapy regimens have been investigated, but a standard of care has not yet been established. Younger patients are generally treated with an intermediate- to high-dose cytarabine-based regimen, and the second remission rate is 30–50%. An anthracycline is often added.[3] Herzig et al. studied the clinical efficacy of high-dose cytarabine in patients with relapsed AML (median age 37 years, 16–60 years) and found that the second CR rate was 47%

with high-dose cytarabine alone and 59% with cytarabine plus an anthracycline.[4] In treatment-resistant patients, the CR rate was significantly worse with high-dose cytarabine alone versus cytarabine plus an anthracycline (20% vs. 56%). Note that the dosage of high-dose cytarabine covered by Japanese National Health Insurance is 2 g/m^2 every 12 h for up to 6 days. The MEC regimen combines mitoxantrone, etoposide, and cytarabine. Drug doses and duration of administration in MEC regimen differ slightly between studies. The second CR rate is 50–60%.[5,6] In a study by Yamamoto et al., the response rate (complete remission including those with incomplete peripheral blood count recovery) for reduced-dose MEC was 36.4%.[7] The FLAG regimen (cytarabine, fludarabine, and G-CSF), a variant of high-dose cytarabine therapy, is another option. In a Japanese phase II study of the FLAGM (cytarabine, fludarabine, G-CSF, and mitoxantrone) regimen for relapsed or refractory AML (median age 52 years, 18–64 years), the CR rate was 73% and 2-year OS was 39.4%.[8]

Options for patients ineligible for intensive chemotherapy are low-dose cytarabine, gemtuzumab ozogamicin (for CD33$^+$ patients), non-intensive chemotherapy such as azacitidine monotherapy or venetoclax combination therapy, and palliative supportive care.[9–14] In a Japanese phase I/II study of gemtuzumab ozogamicin for relapsed or refractory AML, the CR rate was 25% and the rate of remission with incomplete platelet recovery was 5%.[9] Although recent studies have demonstrated the efficacy of fractionated-dose gemtuzumab ozogamicin,[10] the dosage covered by Japanese National Health Insurance is "2 doses of 9 mg/m^2 each, spaced at an interval of at least 14 days." In a retrospective analysis of venetoclax plus a hypomethylating agent (HMA) for relapsed or refractory AML (median age 62 years, 19–81 years), the CR rate was 30%, the response rate was 64%, and the 1-year OS rate was 53%.[13,15]

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CQ12 What are the eligibility criteria for allogeneic HSCT in AML patients not in remission?

Recommendation grade: Category 3

No specific index for determining eligibility for HSCT has been established for patients not in remission who have not been treated with re-induction therapy for relapsed AML. Moreover, no specific index for determining eligibility for HSCT has been established for patients with AML not in remission due to being refractory to induction therapy. At present, it is recommended to determine eligibility for HSCT by comprehensively considering prognostic factors based on retrospective analysis and HSCT-related factors (e.g., donor source) and engaging in shared decision-making with the patient.

Explanation

No study has prospectively compared the clinical effectiveness of allogeneic HSCT and chemotherapy for AML in first relapse. In a retrospective analysis of HSCT outcomes in patients aged 15–60 years with AML in first relapse, Breems et al. identified four prognostic factors (length of relapse-free interval after first remission, cytogenetics at diagnosis, age at relapse, and whether previous HSCT was performed) and classified patients in first relapse into three prognostic groups on the basis of those factors. When they compared HSCT with chemotherapy in only those patients who achieved second remission, they found that HSCT may have yielded superior 5-year OS in all groups.[1] A retrospective analysis of HSCT outcomes in Japanese patients with AML in first relapse found that achieving second remission significantly improves 3-year OS.[2] One study found that performing allogeneic HSCT without re-induction therapy during first relapse, when blast percentages are low, can yield comparable survival rates to HSCT during second remission, but the evidence level of this finding is low.[3] The UK NCRL AML Working Group analyzed data from 8907 patients with AML that did not respond to induction therapy, and found that allogeneic HSCT improves prognosis in patients whose blast percentage did not decrease by at least 50% or remained at 15% or higher after the first induction therapy, or who did not respond to two cycles of induction therapy.[4]

A few studies have reported the outcomes of allogeneic HSCT in AML not in remission, but no index for HSCT eligibility can be easily derived from their results due to the small sample size of many studies and patient selection bias. However, the Center for International Blood and Marrow Transplant Research analyzed 1,673 patients who underwent HSCT for AML not in remission and found that patients can be stratified into groups ranging from a favorable-risk group (3-year OS rate after HSCT: 42%) to an adverse-risk group (3-year OS rate after HSCT: 6%) on the basis of the duration of first remission, the percentage of circulating blasts, donor type, performance status, and the presence of cytogenetic abnormalities.[5] In an analysis of 519 patients with AML who underwent HSCT while not in remission (282 whose induction therapy failed and 237 who relapsed after remission) and who had at least 5% blasts in bone marrow or peripheral blood, Tachibana et al. identified five prognostic factors (CRP, peripheral blood blasts, adverse-risk karyotype, performance status, and unrelated bone marrow donor) and classified patients into four prognostic groups (good, intermediate-1, intermediate-2, and poor). The 2-year OS rates in the intermediate-2 and poor groups were very poor, at 8 and 0%, respectively.[6]

It is recommended to assess not just disease risk but also non-relapse mortality risk based on the EBMT score and HCT-specific comorbidity index (HCT-CI) to make a comprehensive decision on eligibility for allogeneic HSCT.[7]

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CQ13 What treatments are recommended for therapy-related and secondary AML?

Recommendation grade: Category 2A (younger patients [<65 years] eligible for intensive chemotherapy), Category 2B (elderly patients and patients ineligible for intensive chemotherapy)
For younger patients (<65 years) eligible for intensive chemotherapy, it is recommended to achieve remission with chemotherapy, and then perform HSCT when appropriate. For elderly patients and patients ineligible for intensive chemotherapy, venetoclax plus azacitidine combination therapy should be considered.

Explanation

AML is classified into de novo AML and therapy-related/secondary AML based on the type of onset. Therapy-related AML develops due to anti-cancer therapy or radiotherapy for another malignancy, while secondary AML develops through transformation from MDS or a myeloproliferative neoplasm (MPN). Many patients with therapy-related and secondary AML are elderly, and often have cytogenetic abnormalities such as the adverse-risk monosomal or complex karyotype.[1–3] Therefore, outcomes for conventional chemotherapy are poorer in this population than in patients with de novo AML.[1,2] As patients with favorable-risk cytogenetic abnormalities such as t(8;21) and inv(16) still have a significantly poorer prognosis than those with de novo AML, having therapy-related or secondary AML appears to be an independent poor prognostic factor.[1,3]

A cohort analysis was conducted to determine the usefulness of intensive chemotherapy for younger patients (< 65 years). The study compared 38 secondary AML patients enrolled in the EORTC-GIMEMA trials with 114 matched patients with de novo AML and showed no significant differences in CR rate, DFS, or OS.[4] Jentzsch et al. also compared prognosis between 178 patients with therapy-related or secondary AML who underwent allogeneic HSCT in remission and 356 patients with de novo AML, and found that the post-transplant relapse rate among patients classified as favorable risk per the 2017 ELN recommendations was significantly higher for therapy-related/secondary AML than de novo AML, but found no other significant differences in prognosis, and thus did not identify therapy-related/secondary AML as a poor prognostic factor in multivariate analysis.[5] Based on the above evidence, the recommended approach for younger patients (< 65 years) eligible for intensive chemotherapy is to achieve remission with chemotherapy, and then perform HSCT when appropriate.

Another study compared efficacy between high- or intermediate-dose cytarabine-based intensive chemotherapy (IC group), an HMA alone or in combination therapy (HMA group), CPX-351, a dual-drug liposomal encapsulation of daunorubicin and cytarabine, low-dose cytarabine combination therapy, and other investigational drugs in elderly patients (65–75 years) with secondary AML. In that study, the CR rate was significantly lower in the HMA group, but patients treated with low-intensity therapy (HMA or low-dose cytarabine combination therapy) were significantly more likely to have undergone transplantation than those in the IC group (4.3% in the IC group vs. 10.3% in the low-intensity group, $p = 0.001$) and had superior OS (median 6.9 months vs. 5.4 months, $p = 0.048$).[6] These results

demonstrate that simply increasing treatment intensity does not improve outcomes for elderly patients.

A phase III (VIALE-A [M15-656]) trial compared combination therapy with the Bcl-2 inhibitor venetoclax plus azacitidine against venetoclax plus placebo (control group) in newly diagnosed AML patients who were either 75 years or older, or younger than 75 years but ineligible for intensive chemotherapy.[7] A subgroup analysis in secondary AML patients showed that venetoclax plus azacitidine significantly reduced mortality risk (HR 0.56, 95% CI 0.35–0.91). In patients with *TP53* mutations, which are frequently observed in therapy-related AML and secondary AML originating from MPN, the composite CR rate was 55% in the venetoclax plus azacitidine group, compared with 0% in the control group.

Based on the above findings, venetoclax plus azacitidine should be considered for elderly patients and patients ineligible for intensive chemotherapy.

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CQ14 Is maintenance therapy recommended for AML after consolidation therapy or HSCT?

Recommendation grade: Category 2B Maintenance therapy with an FLT3 inhibitor after allogeneic HSCT may improve the prognosis of relapsed or refractory *FLT3*-mutated AML. Indications for maintenance therapy may also expand depending on future circumstances.

Explanation

Based on past evidence, maintenance therapy was previously not recommended for AML other than acute promyelocytic leukemia (APL).[1–4] However, this perception has recently begun to shift in response to new evidence for the efficacy of several drugs in maintenance therapy for non-APL AML.

Wei et al. conducted a phase III double-blind RCT to evaluate the efficacy of oral azacitidine maintenance therapy in AML patients aged 55 years or older who were transplant ineligible, had achieved remission with intensive chemotherapy, and were in the intermediate or adverse cytogenetic risk group.[5] They found that oral azacitidine maintenance therapy was significantly superior to placebo in terms of both OS (median 24.7 months vs. 14.8 months) and DFS (median 10.2 months vs. 4.8 months). Adverse events did not differ between the two groups: patients who received oral azacitidine had a higher incidence of gastrointestinal symptoms and neutropenia, but maintained QOL. Intravenous azacitidine maintenance therapy has also been investigated. In a study of AML patients aged 60 years or older who had achieved remission with intensive chemotherapy, Huls et al. found that treatment with a maximum of 12 maintenance therapy cycles consisting of subcutaneous azacitidine for 5 days every 4 weeks extended DFS, but did not yield a significant difference in OS.[6]

Maintenance therapy with an FLT3 inhibitor after allogeneic HSCT for newly diagnosed *FLT3*-ITD AML is currently being investigated. Burchert et al. conducted a randomized, double-blind trial to investigate the usefulness of sorafenib maintenance for *FLT3*-ITD AML in remission after allogeneic

HSCT, and reported that the maintenance therapy resulted in superior NRM and OS.[7] A similar phase III, randomized, open-label trial of sorafenib maintenance for 180 days post-HSCT also showed favorable results.[8] Results regarding adverse event incidence are inconsistent: one study reported that the patients who underwent sorafenib maintenance had a higher rate of graft-versus-host disease (GVHD) and an increased risk of treatment discontinuation due to toxicity,[7] but another study reports a comparable adverse event profile.[8] In a study of midostaurin maintenance after allogeneic HSCT, the 18-month RFS rate was better in the midostaurin maintenance group than in the control group, but not significantly so (89 vs. 76%, $p=0.27$).[9] Some studies suggest that maintenance therapy with quizartinib or gilteritinib after allogeneic HSCT is effective in relapsed or refractory *FLT3*-ITD AML, though it should be noted that these studies were retrospective.[10–12]

The above evidence supports the efficacy of maintenance therapy after allogeneic HSCT in some patients with AML (transplant-ineligible patients ≥ 55 years who achieved remission with intensive chemotherapy, other than those with favorable-risk cytogenetics) and in patients with newly diagnosed *FLT3*-ITD AML. However, sorafenib for AML and oral azacitidine are currently not approved in Japan; the available options of established maintenance therapies are limited. Future drug approvals and publication of new research results are awaited. Combination therapy with the FLT3 inhibitor quizartinib was shown to be effective in previously untreated *FLT3*-ITD AML[13] and became covered by Japanese National Health Insurance in May 2023. Therefore, administration of quizartinib for 3 years is recommended as maintenance therapy for previously untreated *FLT3*-ITD AML.

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CQ15 Is use of G-CSF recommended in patients with neutropenia after treatment for AML?

Recommendation grade: Category 2B (induction therapy), Category 2A (postremission therapy)
Induction or postremission therapy with G-CSF for AML can shorten the duration of neutropenia and improve quality of life during this phase. It may be considered for elderly patients and patients with severe concomitant infections.

Explanation

Intensification of induction and postremission therapy for AML has improved the remission rate to 80% and 5-year OS rate to around 50% for younger patients. This intensification of therapy was made possible by improvements in the management of hemorrhage and susceptibility to infection due to myelosuppression.

Several phase III trials have investigated whether treatment with G-CSF can prevent infections after induction or postremission therapy for AML.

A phase III trial in younger patients with AML found that G-CSF reduced durations of neutropenia, fever, parenteral antibiotic use, and hospitalization.[1] A Japanese study also found that G-CSF reduced the duration of neutropenia and fever.[2]

Studies in elderly patients with AML, who are prone to severe myelosuppression, have also found that G-CSF reduced the durations of neutropenia, fever, and intravenous antibiotic use.[3,4] Another study found that G-CSF did not reduce mortality but did increase the remission rate.[5]

There have been concerns regarding use of G-CSF in patients with AML because AML cells express G-CSF receptors, but it has been reported that G-CSF does not increase relapse rates or impact long-term survival.[6,7]

Although G-CSF does reduce the duration of neutropenia after induction and postremission therapy for AML, it does not reduce the incidence of severe infection or mortality and does not prolong survival.[8] Therefore, the 2017 ELN recommendations only recommend G-CSF for AML patients with severe concomitant infections or prolonged neutropenia during postremission therapy.[9] However, the American Society of Clinical Oncology guidelines consider use of G-CSF after induction therapy to be reasonable and recommend use of G-CSF after postremission therapy.[10] The NCCN guidelines also state that the use of G-CSF may be considered after postremission therapy, but should be avoided for at least 7 days prior to bone marrow evaluation because it may confound response assessment.[11]

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