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GUIDELINE

JSH practical guidelines for hematological malignancies, 2023: leukemia-4. Chronic myeloid leukemia (CML)/myeloproliferative neoplasms (MPN)

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Overview

Myeloproliferative neoplasms (MPN), a group of diseases that develop through neoplastic transformation at the level of hematopoietic stem cells, are characterized by marked proliferation of myeloid cells (i.e., granulocytes, erythroblasts, and megakaryocytes)[1]. The category of MPN includes chronic myeloid leukemia (CML), chronic neutrophilic leukemia (CNL), polycythemia vera (PV), primary myelofibrosis (PMF), essential thrombocythemia (ET), chronic eosinophilic leukemia (CEL), and MPN, unclassifiable. Early-stage MPN exhibit hyperplasia of bone marrow cells with capacity for differentiation and increased peripheral granulocytes, red blood cells (RBCs), and platelets. Physical findings include splenomegaly and hepatomegaly. MPN produce few subjective symptoms in their early stage, but progress in stages along with general symptoms. They ultimately progress to myelofibrosis or loss of maturation potential through transformation (blast crisis). A different treatment approach is used for CML from those for other types of MPN. These guidelines cover treatments for CML, PV, ET, and PMF.

Chronic myeloid leukemia (CML)

Phases of CML

CML is a type of leukemia that arises from abnormalities in pluripotent hematopoietic stem cells and is characterized by the presence of the Philadelphia (Ph) chromosome formed by the t(9;22)(q34;q11) translocation. This translocation results in the constitutive activation of BCR::ABL1 tyrosine kinase encoded and produced by the *BCR::ABL1* fusion gene on the Ph chromosome. This contributes to the proliferation of leukemic cells and initiates the progression of the disease through three stages [2]. Most cases of CML (85%) are diagnosed during the chronic phase (CP; approximately 3 to 5 years after diagnosis), in which patients have elevated white blood cell (WBC) and platelet counts but exhibit few subjective symptoms. The next phase is the accelerated phase (AP; continues for 3 to 9 months), which is characterized by progressive abnormal differentiation of granulocytes, and

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the final phase is the blast phase (BP; continues for approximately 3 to 6 months), a fatal phase resembling acute leukemia that is characterized by an increase in undifferentiated blasts. The AP and BP are defined according to the European LeukemiaNet (ELN) classification (Table 1) [3].

Prognostic factors of CML

Table 2 shows formulas for prognostic scores that should be assessed at the time of diagnosis along with prognosis according to risk group. Prognosis has conventionally been determined using the Sokal score, which is calculated from four factors: age at presentation, splenomegaly (cm below costal margin), platelet count, and peripheral blasts (%) [4]. More recently, a large study showed that the EUTOS (European Treatment and Outcome Study for CML) long-term survival (ELTS) score [5] correlates with leukemia-related mortality and long-term overall survival (OS) [6]. (http://www.leukemia-net.org/content/leukemias/cml/elts_score/index_eng.html.)

Response assessment for CML treatment

The concept of CML treatment is to control Ph-positive (*BCR::ABL1* +) leukemic cells and prevent progression of disease. Response to treatment is assessed using the 2020 ELN criteria [7].

Response to treatment for CML-CP is assessed at three levels: hematologic response (HR), cytogenetic response (CyR), and molecular response (MR) (Table 3). HR is determined from improvement in peripheral blood findings, CyR from the percentage of Ph-positive cells in the bone marrow, and MR from *BCR::ABL1* expression in blood cells determined by the polymerase chain reaction (PCR) based on the International Scale (IS).

Monitoring of response to treatment for CML

Monitoring of response to treatment for CML with tyrosine kinase inhibitors (TKIs) is conducted using the 2020 ELN recommendations. The following methods are used

Table 1 Phases of CML by the ELN classification

Accelerated phase
Meets any one of the following criteria:
15–29% blasts in peripheral blood or bone marrow, or ≥ 30% blasts and promyelocytes
≥ 20% basophils in peripheral blood
Thrombocytopenia (< 100,000/μL) unrelated to therapy
Chromosomal abnormalities: appearance of additional chromosomal abnormalities (major route: second Ph, trisomy 8, isochromosome 17q, trisomy 19) during therapy
Blast phase
Meets any one of the following criteria:
≥ 30% blasts in peripheral blood or bone marrow
An infiltrative proliferation of blasts in an extramedullary site (apart from spleen)

(From Reference 3)

Table 2 Prognostic scores at diagnosis

Formula for score calculation					Risk group	
Sokal [4]	$\text{Exp}\ 0.0116 \times (\text{age} - 43.4) + 0.0345 \times (\text{spleen} - 7.51) + 0.188 \times [(\text{platelet count}/700)^2 - 0.563] + 0.0887 \times (\text{blood blasts} - 2.10)$				Low risk: < 0.8 Intermediate risk: 0.80–1.2 High risk: > 1.2	
ELTS [5]	$0.0025 \times (\text{age}/10)^3 + 0.0615 \times \text{spleen size} + 0.1052 \times \text{peripheral blood blasts} + 0.4104 \times (\text{platelet count}/1000)^{-0.5}$				Low risk: < 1.5680 Intermediate risk: 1.5680–2.2185 High risk: > 2.2185	
Prognosis [6]	Low risk		Intermediate risk		High risk	
$n = 5154$	Sokal	ELTS	Sokal	ELTS	Sokal	ELTS
%	38	55	38	28	23	13
10-year OS rate	89%	88%	81%	79%	75%	68%
6-year leukemia-related mortality	3%	2%	4%	5%	8%	12%

(From References 4–6)

Table 3 Response assessment criteria for CML

Hematologic response (HR)	Blood and bone marrow test findings and clinical findings
Complete HR (CHR)	1. WBC < 10,000/μL 2. PLT < 450,000/μL 3. No immature cells (blasts, promyelocytes, or myelocytes) in peripheral blood 4. No splenomegaly
Cytogenetic response (CyR)	Percentage of Ph chromosome (*BCR::ABL1*) positive nucleated bone marrow cells
Complete cytogenetic response (CCyR)	0%
Major cytogenetic response (MCyR)	0–35%
Partial cytogenetic response (PCyR)	1–35%
Minor cytogenetic response (minor CyR)	36–65%
Molecular response (MR)	Level of *BCR::ABL1*^{IS}* gene expression (by RT-PCR)
Early molecular response (EMR)	*BCR::ABL1*$^{IS} \leq 10\%$ after 3 months of treatment *BCR::ABL1*$^{IS} \leq 1\%$ after 6 months of treatment
Major molecular response (MMR)	*BCR::ABL1*$^{IS} \leq 0.1\%$
Deep molecular response (DMR)	
$MR^{4.0}$	*BCR::ABL1*$^{IS} \leq 0.01\%$
$MR^{4.5}$	*BCR::ABL1*$^{IS} \leq 0.0032\%$
$MR^{5.0}$	*BCR::ABL1*$^{IS} \leq 0.001\%$

**BCR::ABL1*^{IS}: value standardized to the International Scale (from Reference 7)

for response assessment. CyR is assessed by cytogenetic testing of bone marrow cells, but this can be substituted with fluorescence in situ hybridization (FISH) of peripheral neutrophils. MR is assessed from the level of *BCR::ABL1* expression determined by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) with peripheral blood. The quantitative assessment of *BCR::ABL1* gene expression is based on the ratio to the level of expression of *ABL1* or another gene of interest, standardized to the IS and expressed as *BCR::ABL1*^{IS}. The objective of first-line treatment is to obtain an optimal response, defined as *BCR::ABL1*^{IS} of 10% or lower or partial CyR (PCyR) by 3 months after the start of treatment, *BCR::ABL1*^{IS} of 1% or lower or complete CyR (CCyR) by 6 months, *BCR::ABL1*^{IS} of 0.1% or lower or major MR (MMR) by 12 months, and maintenance of *BCR::ABL1*^{IS} of 0.1% or lower after that point (Table 4). Monitoring should be performed frequently in case of warning, and changing treatments should be considered in case of treatment failure. Even when switching TKIs due to resistance or intolerance to the first-line TKI, the same criteria should be used for response assessment (Table 4). It is important to achieve at least MMR when

Table 4 Response to treatment with TKIs in CML

Timing of evaluation	Response		
	Optimal	Warning	Failure
Pre-treatment	Not specified	High-risk ELTS score, high-risk CCA/Ph +	Not specified
3 months	*BCR::ABL1*$^{IS} \leq 10\%$	*BCR::ABL1*$^{IS} > 10\%$	*BCR::ABL1*$^{IS} > 10\%$ if confirmed within 1–3 months
6 months	*BCR::ABL1*$^{IS} \leq 1\%$	*BCR::ABL1*$^{IS} >$ 1–10%	*BCR::ABL1*$^{IS} > 10\%$
12 months	*BCR::ABL1*$^{IS} \leq 0.1\%$	*BCR::ABL1*$^{IS} >$ 0.1–1%	*BCR::ABL1*$^{IS} > 1\%$
Then, and at any time thereafter	*BCR::ABL1*$^{IS} \leq 0.1\%$*	*BCR::ABL1*$^{IS} >$ 0.1–1%, loss of ≤ 0.1% (MMR)	*BCR::ABL1*$^{IS} > 1\%$, treatment-resistant *ABL1* mutation, high-risk CCA/Ph +

ELTS EUTOS long-term survival. *CCA/Ph +* Clonal chromosomal abnormality in Ph + cells

*A deeper response (DMR) should be targeted if aiming for treatment-free remission (TFR). In this guideline, *BCR::ABL1*$^{IS} \leq 0.0032\%$ ($MR^{4.5}$) is considered an optimal DMR.

(From Reference 7)

treating CML-CP, and quantitative RT-PCR is listed as an essential test in guidelines for CML treatment outside Japan published by organizations such as the ELN [7] and NCCN [8]. Deep molecular response (DMR) is defined as $MR^{4.0}$ at a *BCR::ABL1*^{IS} level of 0.01% or lower, $MR^{4.5}$ at 0.0032% or lower, and $MR^{5.0}$ at 0.001% or lower. In this guideline, DMR is considered to be $MR^{4.5}$ because assessment at this level is covered by Japanese National Health Insurance (NHI).

Specific timing for assessing response to treatment with TKIs is as follows:

(1) Before starting treatment, a complete blood count with differential and cytogenetic testing of bone marrow (G-banding) are performed to determine the proportion of Ph-positive cells and whether additional chromosomal abnormalities are present. *BCR::ABL1* mRNA is also quantified to confirm pre-treatment levels. If *BCR::ABL1* cannot be detected by quantitative RT-PCR to determine *BCR::ABL1*^{IS} despite the patient having Ph-positive cells on cytogenetic testing of bone marrow or testing positive for the *BCR::ABL1* fusion gene on FISH, the BCR breakpoint may be in an unusual location, and its location must be confirmed by a method such as direct sequencing.
(2) During the period immediately following the start of treatment, a complete blood count with differential is performed once every week to once every 2 weeks.
(3) Quantitative RT-PCR to determine *BCR::ABL1*^{IS} is performed with peripheral blood at the initial visit and then every 3 months until achievement of MMR. After achievement of MMR, it is performed every 3 to 6 months.
(4) In the event of a marked increase in *BCR::ABL1*^{IS} or treatment failure as defined by the 2020 ELN criteria, staging should be reconfirmed by bone marrow tests and additional chromosomal abnormalities assessed by cytogenetic testing of bone marrow. *BCR::ABL1* point mutation analysis (not covered by Japanese NHI) can provide useful information for determining the treatment plan.

Goal of treatment for CML

To date, the goal of treatment for CML has been no progression to blast crisis. However, it is now possible to achieve a long-lasting DMR in many patients through TKI therapy. Consequently, the goal of treatment is now beginning to shift to achievement of long-term treatment-free remission (TFR). In an imatinib discontinuation trial, some patients who had maintained DMR for at least 2 years after long-term imatinib therapy achieved long-term TFR [9]. In addition, all patients who lost DMR after discontinuation of imatinib regained DMR after resuming imatinib. Although further clinical trials are warranted to validate the feasibility of treatment discontinuation after achievement of DMR on a TKI, the position of these guidelines is that the discontinuation of TKI is acceptable in routine practice under careful supervision by a specialist. As a reference, these guidelines, as with the 2020 ELN recommendations [7] and NCCN guidelines, [8] mention requirements for discontinuation and the importance of periodic monitoring after discontinuation when discontinuing TKIs outside a clinical trial.

Ph-negative myeloproliferative neoplasm (MPN)

Mutations that cause constitutive activation of the JAK–STAT signaling pathway are observed consistently in PV, ET, and PMF. Mutations in *JAK2* are observed in over 95% of patients with PV and about half of patients with ET and PMF, mutations in the thrombopoietin receptor gene MPL are observed in 3 to 8% of patients with ET and PMF, and mutations in calreticulin (CALR) are observed in 20 to 30% of patients with ET and PMF and cause chaotic proliferation of blood cells [10].

PV, ET, and PMF share general symptoms such as fever, weight loss, malaise, pruritus, and bone pain, and are prone to complication by thrombosis. Thrombosis has been reported to occur at a rate of 5.3 cases per 100 patient-years in PV, 4 to 8 in ET, and 2.23 in PMF, and is a major cause of death in PV and ET. MPNs also transform to acute myeloid leukemia (AML) in some patients. Eight-year survival rates for PV and ET are relatively favorable compared with the general population at 0.84 (0.77–0.90) and 0.91 (0.84–0.97), [11] but median survival for PMF is a poor 3.8 years [12]. Therefore, treatment selection should be aimed at preventing thrombosis for PV and ET, but at extending survival for PMF.

Polycythemia vera (PV)

Prognostic classification for PV [13]

The survival prognosis of PV is relatively favorable, and median survival of at least 10 years after treatment can be expected. Therefore, the primary focus of treatment is prevention of thromboembolic complications. Patients aged 60 years or older and patients with a history of thrombosis are classified as being at high risk for thrombosis (Table 5) [13, 14].

Summary of treatments for PV of treatments for PV

(1) If patients have general risk factors for thrombosis such as hypertension, dyslipidemia, obesity, and diabetes, treatment for these conditions should be performed.

(2) Phlebotomy plus low-dose aspirin is selected for patients at low risk for thrombosis (age < 60 years and no history of thrombosis).
(3) Cytoreductive therapy is added to phlebotomy plus aspirin for high-risk patients.

Essential thrombocythemia (ET)

Prognostic classification for ET

ET has a favorable survival prognosis, and patients can be expected to live nearly as long as their healthy counterparts. Therefore, the primary focus of treatment is prevention of thromboembolic complications. Patients aged 60 years or older and patients with a history of thrombosis are classified as being at high risk for thrombosis [15]. A risk classification system that incorporates *JAK2* mutations was recently proposed (Table 6) [14–16]. There is no consensus regarding whether or not WBC count, platelet count, or risk factors for cardiovascular lesions (e.g., hypertension, dyslipidemia, diabetes, and smoking) should be considered risk factors for thrombosis.

The survival prognosis is generally favorable, and a three-group risk classification system on the basis of factors such as age, WBC count at presentation, and history of thrombosis has been proposed (Table 7) [17, 18].

Table 5 Classification of thrombosis risk in patients with PV

Author	Prognostic factors	Risk classification
Barbui T et al. [14]	Age < 60 years and no history of thrombosis	Low risk
	Age ≥ 60 years or history of thrombosis	High risk
Tefferi A et al. [13]	Age < 60 years No history of thrombosis Platelet count < 1,500,000/μL No risk factors for cardiovascular disease (smoker, hypertension, congestive heart failure) Meets all of the above criteria:	Low risk
	Not classified into low- or high-risk group	Intermediate risk
	Age ≥ 60 years or history of thrombosis	High risk

Table 6 Classification of thrombosis risk in patients with ET

Author	Prognostic factors		Risk classification
Barbui T et al. [14]	Age < 60 years and no history of thrombosis		Low risk
	Age ≥ 60 years or history of thrombosis		High risk
Ruggeri M et al. [15]	Age < 60 years, no history of thrombosis, and platelet count < 1,500,000/μL		Low risk
	Age ≥ 60 years, history of thrombosis, or platelet count ≥ 1,500,000/μL		High risk
Barbui T et al. [16]	Age < 60 years and no history of thrombosis	No *JAK2* mutation	Very low risk
		JAK2 mutation	Low risk
	Age ≥ 60 years, no history of thrombosis, and no *JAK2* mutation		Intermediate risk
	Age ≥ 60 years and *JAK2* mutation		High risk
	History of thrombosis		

Table 7 Risk classification for predicting survival in patients with ET

Author	Prognostic factors	Risk classification	Median survival (years)
Wolanskyj et al. [17]	Age < 60 years and WBC count < 15,000/μL	Low risk	25.3
	Age ≥ 60 years or WBC count ≥ 15,000/μL	Intermediate risk	16.9
	Age ≥ 60 years and WBC count ≥ 15,000/μL	High risk	10.3
Passamonti et al. [18]	Age ≥ 60 years (2)	Low risk (0)	Not reached
	WBC ≥ 11,000/μL (1)	Intermediate risk (1, 2)	24.5
	History of thrombosis (1)	High risk (3, 4)	13.8

Summary of treatments for ET

(1) Patients at low risk of thrombosis should be observed periodically.
(2) Patients at high risk of thrombosis should be treated with a combination of low-dose aspirin and cytoreductive therapy to prevent thromboembolic complications [19].

Primary myelofibrosis (PMF) and post-polycythemia vera/post-essential thrombocythemia myelofibrosis (post-PV/ET-MF)

Prognostic classification for myelofibrosis (MF)

For PMF, three versions of the International Prognostic Scoring System (IPSS), which are based on clinical data, and prognostic classification systems that integrate chromosomal abnormalities with mutation or clinical data have been reported. Among these classification systems, in the original IPSS, which comprises the 5 prognostic factors of age (> 65 years), clinical symptoms (e.g., weight loss, night sweats, and fever), hemoglobin (Hb) level (< 10g/dL), WBC count at diagnosis (> 25,000/μL), and peripheral blast percentage (≥ 1%); [20] the Dynamic IPSS (DIPSS), which assigns different weights to these 5 factors; [21] and the DIPSS Plus, which adds cytogenetic abnormalities, platelet count, and transfusion dependence to the DIPSS, [22] the total score is used to classify the patient into one of four risk groups: Low, Intermediate-1 (Int-1), Intermediate-2 (Int-2), or High. These systems are useful for predicting the prognosis in Japanese patients with PMF (Table 8) [20–23]. The Myelofibrosis Secondary to PV and ET Prognostic Model (MYSEC-PM), which stratifies patients into four groups according to a score based on six independent unfavorable prognostic factors (age, Hb < 11 g/dL, peripheral blasts ≥ 3%, platelets < 150,000/μL, constitutional symptoms, and absence of *CALR* mutation) has been shown to be useful for predicting prognosis in post-PV/ET-MF [23].

Summary of treatments for PMF and post-PV/ET-MF

(1) Treatment for Low and Int-1 risk groups: patients without clinical symptoms or anemia should be observed

Table 8 Prognostic models for PMF and post-PV/ET-MF

Prognostic model	Unfavorable prognostic factors (score)	Prognostic evaluation		
		Total score	Risk classification	Median survival (years)
IPSS [21]	Age > 65 years (1) Persistent fever, night sweats, and/or weight loss (1) Hb < 10 g/dL (1) WBC > 25,000/μL (1) Peripheral blasts ≥ 1% (1)	0 1 2 ≥ 3	Low risk Intermediate-1 risk Intermediate-2 risk High risk	11.3 7.9 4.0 2.3
DIPSS/aaDIPSS [21]	DIPSS: Age > 65 years (1) Persistent fever, night sweats, and/or weight loss (1) Hb < 10 g/dL (2) WBC > 25,000/μL (1) Peripheral blasts ≥ 1% (1)	0 1–2 3–4 5–6	Low risk Intermediate-1 risk Intermediate-2 risk High risk	Not reached 14.2 4.0 1.5
	Age-adjusted DIPSS (< 65 years): Persistent fever, night sweats, and/or weight loss (2) Hb < 10 g/dL (2) WBC > 25,000/μL (1) Peripheral blasts ≥ 1% (2)	0 1–2 3–4 ≥ 5	Low risk Intermediate-1 risk Intermediate-2 risk High risk	Not reached 9.8 4.8 2.3
DIPSS plus [22]	Unfavorable karyotypes (complex karyotype [≥ 3 abnormalities], + 8, -7/7q-, i(17q), -5/5q-, 12p-, inv(3), or 11q23 abnormality) (1) Platelets < 100,000/μL (1) Need for transfusions (1) DIPSS Intermediate-1 risk (1) DIPSS Intermediate-2 risk (2) DIPSS High risk (3)	0 1 2–3 4–6	Low risk Intermediate-1 risk Intermediate-2 risk High risk	15.4 6.5 2.9 1.3
MYSEC-PM [23]	Age (0.15/year) Persistent fever, night sweats, and/or weight loss (1) Hb < 11g/dL (2) Platelets < 150,000/μL (1) Peripheral blasts ≥ 3% (2) No *CALR* mutation (2)	< 11 ≥ 11 to < 14 ≥ 14 to < 16 ≥ 16	Low risk Intermediate-1 risk Intermediate-2 risk High risk	Not reached

without intervention because survival time in this group is over 10 years. Patients with splenomegaly or general symptoms are treated with ruxolitinib.

(2) Treatment for Int-2 and High-risk groups: allogeneic hematopoietic stem cell transplantation (allo-HSCT) is the only curative treatment option at present, and is recommended for patients who do not have comorbidities and have a suitable donor. Patients not eligible for allo-HSCT are treated with ruxolitinib.

(3) Anemia is treated with RBC transfusions or anabolic steroids.

References

1. Arber DA, et al. Introduction and overview of the classification of myeloid neoplasms. Swerdlow SH, et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, IARC; 2017: pp16-27. **(Textbook)**

2. Vardiman JW, et al. Chronic myeloid leukaema, BCR-ABL1-positive. Swerdlow SH, et al. eds. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Lyon, IARC; 2017: pp30-6. **(Textbook)**

3. Baccarani M, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122(6): 872–84. **(Review)**

4. Sokal JE, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984; 6(3 4): 789–99. **(3iA)**

5. Pfirrmann M, et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016; 30(1): 48–56. **(3iA)**

6. Geelen IGP, et al. Validation of the EUTOS long-term survival score in a recent independent cohort of "real world" CML patients. Leukemia. 2018; 32(10): 2299–303. **(3iA)**

7. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–84. **(Review)**

8. Deininger MW, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020; 18(10): 1385–415. **(Review)**

9. Etienne G, et al. Long-Term Follow-Up of the French Stop Imatinib (STIM1) Study in Patients With Chronic Myeloid Leukemia. J Clin Oncol. 2017; 35(3): 298–305. **(3iiiDiv)**

10. Vainchenker W, et al. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. Blood. 2017; 129(6): 667–79. **(Review)**

11. Hultcrantz M, et al. Patterns of survival among patients with myeloproliferative neoplasms diagnosed in Sweden from 1973 to 2008: a population-based study. J Clin Oncol. 2012; 30(24): 2995–3001. **(3iA)**

12. Takenaka K, et al. Clinical features and outcomes of patients with primary myelofibrosis in Japan: report of a 17-year nationwide survey by the Idiopathic Disorders of Hematopoietic Organs Research Committee of Japan. Int J Hematol. 2017; 105(1): 59–69. **(3iA)**

13. Tefferi A, et al. Polycythemia vera: scientific advances and current practice. Semin Hematol. 2005; 42(4): 206–20. **(Review)**

14. Barbui T, et al. Philadelphia-negative classical myeloproliferative neoplasms: critical concepts and management recommendations from European LeukemiaNet. J Clin Oncol. 2011; 29(6): 761–70. **(Review)**

15. Ruggeri M, et al. No treatment for low-risk thrombocythaemia: results from a prospective study. Br J Haematol. 1998; 103(3): 772–7. **(2C)**

16. Barbui T, et al. Practice-relevant revision of IPSET-thrombosis based on 1019 patients with WHO-defined essential thrombocythemia. Blood Cancer J. 2015; 5(11): e369. **(3iiDi)**

17. Wolanskyj AP, et al. Essential thrombocythemia beyond the first decade: life expectancy, long-term complication rates, and prognostic factors. Mayo Clin Proc. 2006; 81(2): 159–66. **(3iiA)**

18. Passamonti F, et al. A prognostic model to predict survival in 867 World Health Organization-defined essential thrombocythemia at diagnosis: a study by the International Working Group on Myelofibrosis Research and Treatment. Blood. 2012; 120(6): 1197–201. **(3iiA)**

19. Palandri F, et al. Long-term follow-up of 386 consecutive patients with essential thrombocythemia: safety of cytoreductive therapy. Am J Hematol. 2009; 84(4): 215–20. **(3iiA)**

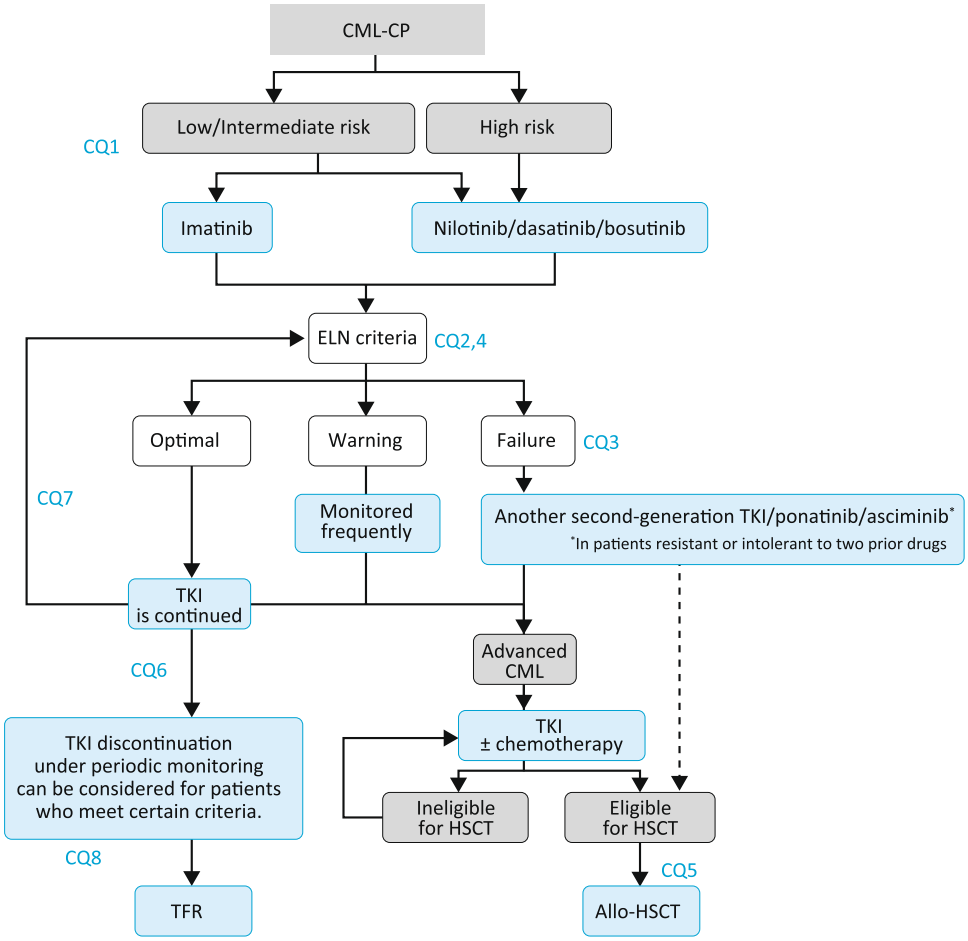
20. Cervantes F, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009; 113(13): 2895–901. **(3iiA)**

21. Passamonti F, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010; 115(9): 1703–8. **(3iiA)**

22. Gangat N, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011; 29(4): 392–7. **(3iiA)**

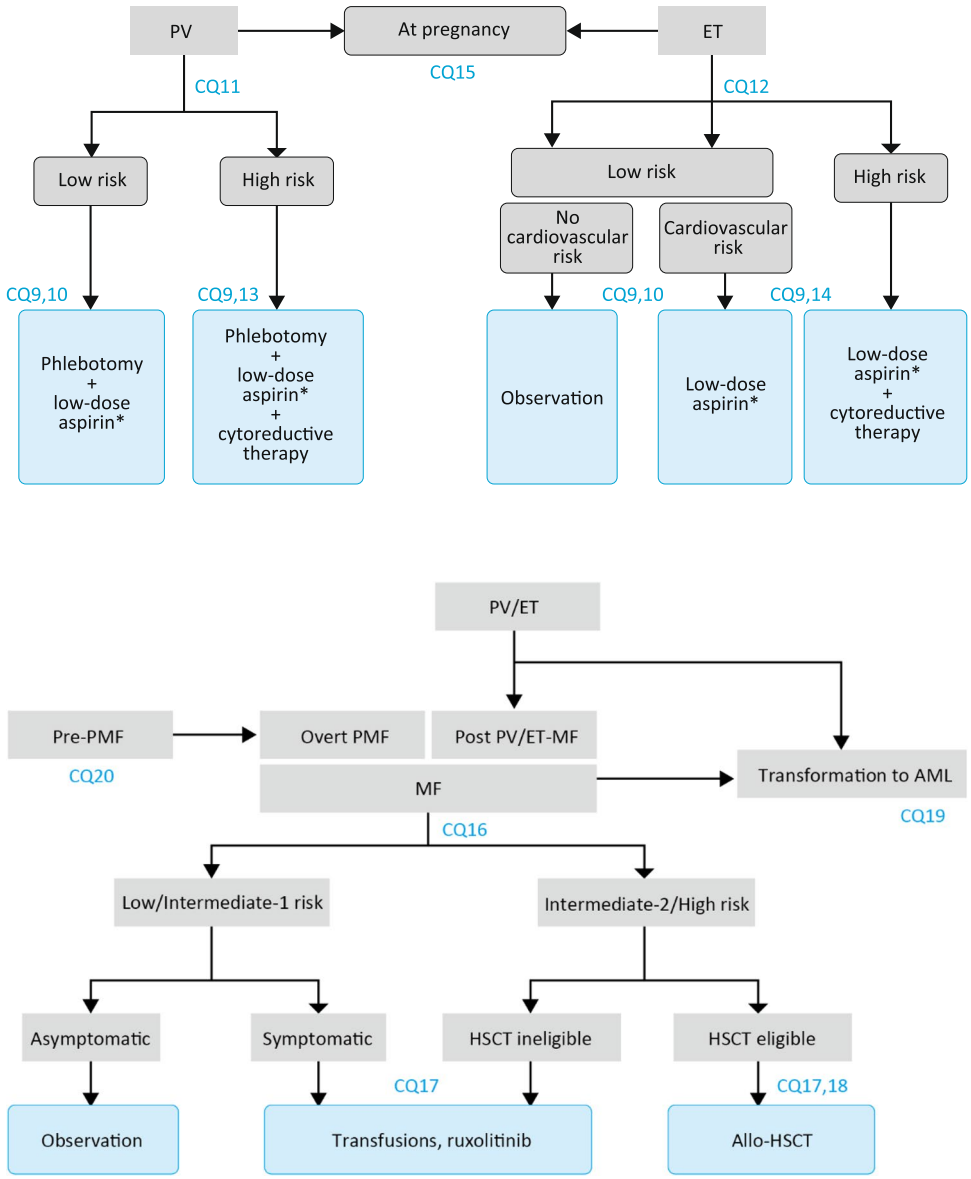
23. Passamonti F, et al. A clinical-molecular prognostic model to predict survival in patients with post-polycythemia vera and post-essential thrombocythemia myelofibrosis. Leukemia. 2017; 31(12): 2726–31. **(3iiA)**

Algorithm



Algorithm for CML

TKIs are currently the key drug for CML treatment. CML-CP is treated with a TKI (imatinib, nilotinib, dasatinib, or bosutinib) selected with consideration to risk and patient characteristics (CQ1). If an optimal response is achieved after treatment is started, treatment is continued. In case of warning, frequent monitoring is performed (CQ2). In case of failure, treatment is switched to another second-generation TKI or ponatinib, or to asciminib in patients resistant or intolerant to two prior drugs (CQ3). High-risk patients should be identified and monitored to prevent cardiovascular adverse reactions associated with long-term TKI use (CQ4). Advanced CML that has progressed from CML-CP is treated with a TKI alone or in combination with chemotherapy for acute leukemia. Allo-HSCT is recommended in patients eligible for transplantation (CQ5). TFR is a new goal for CML treatment, and TKI discontinuation under periodic monitoring can be considered for patients who meet certain criteria (CQ6). The TKI dose can be reduced if necessary due to adverse events, age, or other patient characteristics. In patients maintaining DMR, the TKI dose may be reduced to avoid TKI-related adverse events (CQ7).



Algorithm for MPN

The treatment approach for PV, ET, or PMF should be based on risk assessment.

The goal of treatment for PV and ET is to prevent thrombosis and hemorrhage. Low-dose aspirin and phlebotomy are effective for PV patients in all risk categories (CQ9). Cytoreductive therapy is not recommended for low-risk PV (CQ10), but recommended for high-risk PV. The therapeutic target for hematocrit is less than 45% (CQ11, 13). Ruxolitinib is beneficial for patients refractory or intolerant to hydroxyurea. Observation is the general approach for low-risk ET patients (< 60 years and no history of thrombosis), but antiplatelet therapy (with aspirin) is recommended for low-risk ET patients with cardiovascular risk factors (smoking, hypertension, dyslipidemia, and diabetes) or *JAK2* mutations to reduce risk of thrombosis (CQ9). Cytoreductive therapy is not recommended for low-risk ET (CQ10). High-risk patients with ET (≥ 60 years or history of thrombosis) are treated with low-dose aspirin and cytoreductive therapy. Hydroxyurea and anagrelide are options for cytoreductive therapy (CQ14). The therapeutic target for platelets in ET is not clear, but is often set at 400,000 to 600,000/μL in clinical trials (CQ12). When treating pregnant patients with PV/ET, intervention with low-dose aspirin is recommended. Concomitant low molecular weight heparin (not covered by Japanse NHI) should be considered if the pregnancy is high-risk (CQ15).

MF consists of PMF and secondary MF that progressed from PV/ET. The treatment plan should be determined based on the risk classification (CQ16). The survival prognosis of MF is relatively good for the Low and Int-1 risk groups. The objective of treatment when symptoms such as anemia, general malaise, and bloating associated with splenomegaly are present is to alleviate those symptoms (CQ17). Observation without treatment is advisable for asymptomatic patients. Allo-HSCT should be considered for Int-2 and High-risk group patients without comorbidities who have a suitable donor because the survival prognosis for these groups is unfavorable (CQ18). Allo-HSCT is the curative treatment option for MF. In patients ineligible for HSCT, ruxolitinib can be expected to reduce splenomegaly and general symptoms, as well as to improve the survival prognosis (CQ17). For leukemic transformation of MF, induction therapy should be performed with a usual AML regimen, and allo-HSCT should be considered for transplant-eligible patients (CQ19).

Fibrosis is not observed in the early stage of PMF (pre-PMF), but the disease progresses into overt PMF with marked fibrosis. Although there is little evidence regarding treatment of pre-PMF, it is recommended to select a treatment approach based on risk of overt PMF (CQ20). Thromboprophylaxis should be considered for patients with a history of thrombosis or cardiovascular risk (CQ9).

CQ 1 What is recommended for treatment of newly diagnosed CML-CP?

Recommendation grade: Category 1 The first-generation TKI imatinib (400 mg once daily [QD]) and the second-generation TKIs nilotinib (300 mg twice daily [BID]), dasatinib (100 mg QD), and bosutinib (400 mg QD) are recommended for treatment of newly diagnosed CML-CP.
Recommendation grade: Category 2A Treatment with a second-generation TKI is advisable for high-risk patients, such as those with a high Sokal score before treatment. The four drugs have different adverse reaction profiles, and thus it is recommended to select an appropriate drug with consideration to comorbidities and other patient characteristics.

Explanation

A trial comparing the first-generation TKI imatinib with combination of chemotherapy and interferon alpha (IFN-α) in newly diagnosed CML-CP (the IRIS trial) demonstrated the superiority of imatinib [1]. The long-term efficacy and safety of imatinib have also been shown: the 8-year OS rate was 85% (93% when only CML-related deaths were considered) and the 10-year OS rate was 83.3% [2, 3]. Similar results were confirmed in a clinical trial (Japan Adult Leukemia Study Group [JALSG] CML202 study) in Japanese patients (7-year OS rate: 93%) [4]. Later trials compared high-dose (600–800 mg QD) imatinib with standard-dose (400 mg QD) imatinib but found no clear efficacy or safety benefit for high-dose imatinib [5].

Results of phase III trials comparing the second-generation TKIs nilotinib, dasatinib, and bosutinib against a control of imatinib have been published. Treatment with nilotinib 300 mg BID (ENESTnd trial), [6] dasatinib 100 mg QD (DASISION trial), [7] or bosutinib 400 mg QD (BFORE trial) [8] yielded superior rates of CCyR and MMR at 12 months compared with imatinib 400 mg QD. Although OS did not differ significantly, the rate of progression to AP/BP was low, and the ENESTnd trial showed a significant decrease in CML-related mortality [9–11]. The above evidence demonstrates that second-generation TKIs have superior efficacy to imatinib. On the basis of these results, treatment with a second-generation TKI is considered advisable for high-risk patients, such as those with a high Sokal score before treatment. There is no consensus regarding which second-generation TKI should be used first because no study has directly compared second-generation TKIs [12]. However, in patients observed long-term, incidence of cardiovascular events is higher with second-generation TKIs than with imatinib [9, 10]. The four TKIs have different adverse reaction profiles, and thus it is recommended to select an appropriate first-line drug with consideration to comorbidities and other patient characteristics.

References

1. O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348(11): 994–1004. **(1iiDiv)**

2. Deininger M, et al. International Randomized Study of Interferon vs STI571(IRIS) 8-Year Follow-up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia

in Chronic Phase (CML-CP) Treated with Imatinib. Blood. 2009; 114(22): 1126. **(2Diii)**

3. Hochhaus A, et al. Long-Term Outcomes of Imatinib Treatment for Chronic Myeloid Leukemia. N Engl J Med. 2017; 376(10): 917–27. **(2A)**

4. Ohnishi K, et al. Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: the JALSG CML202 study. Cancer Sci. 2012; 103 (6): 1071–8. **(2Div)**

5. Gafter-Gvili A, et al. High-dose imatinib for newly diagnosed chronic phase chronic myeloid leukemia patients–systematic review and meta-analysis. Am J Hematol. 2011; 86(8): 657–62. **(1iiA,D)**

6. Saglio G, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010; 362(24): 2251–9. **(1iiDiv)**

7. Kantarjian H, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010; 362(24): 2260–70. **(1iiDiv)**

8. Cortes JE, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018; 36(3): 231–37. **(1iiDiv)**

9. Hochhaus A, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016; 30(5): 1044–54. **(1iiDiv)**

10. Cortes JE, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016; 34(20): 2333–40. **(1iiDiv)**

11. Brümmendorf TH, et al. Bosutinib versus imatinib for newly diagnosed chronic phase chronic myeloid leukemia: final results from the BFORE trial. Leukemia. 2022; 36(7): 1825–33. **(1iiDiv)**

12. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–84. **(Review)**

CQ 2 What is the recommended method for monitoring response to TKI therapy?

Recommendation grade: Category 1
It is recommended to monitor *BCR::ABL1* standardized to the IS ($BCR::ABL1^{IS}$) by quantitative RT-PCR before TKI therapy and every 3 months after starting TKI therapy.

Explanation

Response monitoring for CML has conventionally been based on the percentage of Ph chromosomes determined by G-banding chromosome analysis of bone marrow, the percentage of *BCR::ABL1* positive cells determined by FISH, and the *BCR::ABL1* mRNA copy number determined by RT-PCR. Almost all patients treated with a TKI such as imatinib achieve MR, and thus the ELN recommendations have listed quantitative RT-PCR with peripheral blood as the main method for response assessment since the 2013 edition [1]. The 2013 ELN recommendations also listed cytogenetic analysis alongside quantitative RT-PCR as another option for countries where quantitative RT-PCR cannot be performed following standardized methods, [1] but the 2020 ELN recommendations only include quantitative RT-PCR [2]. The method for quantitative RT-PCR recommended in these guidelines is to determine the ratio of the mRNA copy number of *BCR::ABL1* to the mRNA copy number of a reference gene such as *ABL* and standardize that ratio to the IS. This figure is expressed as $BCR::ABL1^{IS}$. In Japan, quantitative RT-PCR to determine $BCR::ABL1^{IS}$ became covered by NHI in April 2015, and this test is recommended at the start of TKI treatment and every 3 months thereafter [2]. However, it is important to be aware that this test may not detect rare *BCR::ABL1* variants with a breakpoint other than e13a2(b2a2) or e14a2(b3a2).

Subset analysis in the IRIS study showed very favorable outcomes for patients who achieved an MMR ($BCR::ABL1^{IS} \leq 0.1\%$) at 18 months of treatment with imatinib as evidenced by the 7-year event-free survival (EFS) rate of 95% and 7-year progression-free survival (PFS) rate of 99%. There have been no reports of a patient who achieved MMR at 12 months after starting imatinib therapy progressing to CML-AP/BP sooner than 8 years, [3–5] and thus MMR determined by quantitative RT-PCR has become established as a surrogate marker for predicting long-term survival. Phase III trials comparing the second-generation TKIs nilotinib and dasatinib against a control of imatinib (ENESTnd [6, 7] and DASISION [8, 9] trials) showed that early molecular response (EMR) defined as $BCR::ABL1^{IS} \leq 10\%$ after 3 months of treatment is a surrogate marker that predicts 5-year PFS and 5-year OS regardless of the TKI used. Similarly, the NEW TARGET study, an observational study in Japanese patients with CML-CP, showed that achieving EMR after 3 months of treatment was a predictor of good 5-year PFS regardless of the TKI used [10].

References

1. Baccarani M, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013; 122(6): 872–84. **(Review)**

2. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–84. **(Review)**

3. Druker BJ, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med. 2006; 355(23): 2408–17. **(2Diii)**

4. Huges TP, et al. Long-term prognostic significance of early molecular response to imatinib in newly diagnosed chronic myeloid leukemia: an analysis from the International Randomized Study of Interferon and STI571(IRIS). Blood. 2010; 116(19): 3758–65. **(2Diii)**

5. Deininger M, et al. International Randomized Study of Interferon vs STI571(IRIS) 8-Year Follow-up: Sustained Survival and Low Risk for Progression or Events in Patients with Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Treated with Imatinib. Blood. 2009; 114 (22): 1126. **(2Diii)**

6. Saglio G, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med. 2010; 362(24): 2251–9. **(1iiDiv)**

7. Hochhaus A, et al. Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial. Leukemia. 2016; 30(5): 1044- 54. **(1iiDiv)**

8. Kantarjian H, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2010; 362(24): 2260–70. **(1iiDiv)**

9. Cortes JE, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016; 34(20): 2333–40. **(1iiDiv)**

10. Kizaki M, et al.; New TARGET investigators. Efficacy and safety of tyrosine kinase inhibitors for newly diagnosed chronic-phase chronic myeloid leukemia over a 5-year period: results from the Japanese registry obtained by the New TARGET system. Int J Hematol. 2019; 109(4): 426–39. **(3iiiA)**

CQ 3 What are the recommended second, third, and later-line therapies after a response of warning or failure according to the ELN response assessment criteria?

Recommendation grade: Category 2A

- Treatment with a second-generation TKI not previously used (nilotinib, dasatinib, or bosutinib), selected with consideration to results of *ABL1* point mutation analysis, is recommended as second-line therapy for CML-CP.
- Treatment with a second-generation TKI not previously used, a third-generation TKI (ponatinib), or a STAMP inhibitor (asciminib), selected with consideration to results of *ABL1* point mutation analysis, is recommended as third- and later-line therapy for CML-CP.
- Ponatinib is recommended if T315I mutation is detected by *ABL1* point mutation analysis.

Explanation

Second-line therapy

Response to first-line therapy is assessed per the 2020 ELN criteria [1]. If the response is warning, the patient is monitored frequently to ascertain whether the response is optimal or failure before the next evaluation timepoint in 3 months. Confirming whether adherence has decreased or treatment was interrupted due to adverse reactions and performing pharmacokinetic tests (e.g., evaluation of trough concentration) also informs assessment of resistance to treatment. When the response is warning, changing the TKI is optional, and the decision is made with consideration to the patient's age, comorbidities, and tolerance of treatment, and whether the goal of treatment is TFR. However, changing the TKI is essential if the response is failure. First, testing for ABL1 kinase domain point mutations and additional chromosomal abnormalities is performed, and a second-generation TKI (nilotinib, dasatinib, or bosutinib) is then selected as an appropriate second-line therapy depending on which mutations were detected [2]. Response to second-line therapy is assessed using the same criteria used for first-line therapy [1].

A phase II trial in which patients resistant or intolerant to imatinib were switched to nilotinib 400 mg BID showed favorable outcomes after 48 months of follow-up (CCyR rate: 45%, 4-year OS rate: 78%) [3]. In the final report from a phase III trial in which patients resistant or intolerant to imatinib were randomly assigned a dasatinb dose of 100 mg

QD, 50 mg BID, 140 mg QD, or 70 mg BID, outcomes at the 7-year mark were favorable in the 100 mg QD group (MMR rate: 46%, PFS rate: 42%, OS rate: 65%) and comparable in the other dose groups [4]. A phase I/II trial in which 286 patients resistant or intolerant to imatinib were switched to bosutinib showed favorable outcomes after 4 years of follow-up (cumulative CCyR rate: 49%, 2-year OS rate: 91%) [5].

Third- and later-line therapy

Ponatinib and asciminib have been shown to be beneficial in CML resistant or intolerant to two or more TKIs. Switching to ponatinib 45 mg QD yielded a CCyR rate of 46% and an MMR rate of 34% in a phase II trial (PACE trial) within 1 year of treatment in patients with TKI-resistant/intolerant CML heavily pretreated with second-generation TKIs and patients with the T315I mutation, [6] and in the final report at the 5-year mark, the MMR rate was 40%, MR4.5 rate was 24%, and OS rate was 73% [7].

Asciminib, which became commercially available in 2022, is a first-in-class STAMP (specifically targeting the ABL myristoyl pocket) inhibitor that differs from conventional ATP-competitive TKIs in that it inhibits ABL1 kinase by binding to the myristoyl pocket of ABL1. A randomized phase III trial of asciminib 40 mg BID versus bosutinib 500 mg QD for CML-CP resistant/intolerant to two or more TKIs (ASCEMBL trial) showed that asciminib had superior efficacy and safety (24-week MMR rate: 25.5% vs. 13.2%, rate of treatment discontinuation due to adverse events: 5.8% vs. 21.1%) [8].

T315I mutation

If point mutation analysis of the ABL1 kinase domain shows a T315I mutation, ponatinib should be selected because all second-generation TKIs are ineffective against this mutation. In the abovementioned PACE trial of ponatinib, the 5-year MMR rate was 58% and OS rate was 66% among patients with the T315I mutation at baseline, indicating that long-term treatment efficacy was not inferior [7]. In the phase I trial of asciminib, 5 of 18 CML-CP patients (28%) who were T315I-positive after treatment with at least one TKI achieved MMR within one year [9]. On the basis of these results, high-dose asciminib (200 mg BID) became the treatment of choice for T315I-positive patients, and the additional indication for T315I-positive patients was approved in the United States, but remains unapproved in Japan. The efficacy of asciminib 40 mg BID in T315I-positive patients is unknown because the ASCEMBL trial excluded patients with the T315I mutation.

References

1. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–84. **(Review)**

2. Gambacorti-Passerini C, et al. Chronic myeloid leukemia: Second-line drugs of choice. Am J Hematol. 2016; 91(1): 67–75. **(Review)**

3. Giles FJ, et al. Nilotinib in imatinib-resistant or imatinib-intolerant patients with chronic myeloid leukemia in chronic phase: 48-month follow-up results of phase II study. Leukemia. 2013; 27(1): 107–12. **(3iiiDiv)**

4. Shah NP, et al. Dasatinib in imatinib-resistant or -intolerant chronic-phase, chronic myeloid leukemia patients: 7-year follow-up of study CA180-034. Am J Hematol. 2016; 91(9): 869–74. **(3iiiDiv)**

5. Brümmendorf TH, et al. Factors influencing long-term efficacy and tolerability of bosutinib in chronic phase chronic myeloid leukaemia resistant or intolerant to imatinib. Br J Haematol. 2016; 172(1): 97–110. **(3iiiDiv)**

6. Cortes JE, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med. 2013; 369(19): 1783–96. **(3iiiDiv)**

7. Cortes JE, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018; 132(4): 393–404. **(3iiiDiv)**

8. Réa D, et al. A phase 3, open-label, randomized study of asciminib, a STAMP inhibitor, vs bosutinib in CML after 2 or more prior TKIs. Blood. 2021; 138(21): 2031–41. **(1iiDiv)**

9. Hughes TP, et al. Asciminib in Chronic Myeloid Leukemia after ABL Kinase Inhibitor Failure. N Engl J Med. 2019; 381(24): 2315–26. **(3iiiDiv)**

CQ 4 What is the recommended method for monitoring for late adverse reactions of concern during TKI therapy?

Recommendation grade: Category 2B
It is necessary to evaluate risk factors for cardiovascular events (age, sex, blood pressure, lipid levels, diabetes, and smoking history) and periodically test patients for atherosclerosis and pulmonary arterial hypertension before and during TKI therapy. Periodic testing for chronic kidney disease (CKD) is also necessary.

Explanation

Long-term TKI use can cause complications such as serious cardiovascular events (ischemic heart disease, pulmonary arterial hypertension [PAH], peripheral arterial disease, cerebral infarction) and CKD.

Over the 10-year observation period in the ENESTnd trial and 5-year observation period in the DASISION trial, the incidence of cardiovascular adverse reactions was higher with second-generation TKIs (nilotinib and dasatinib) than the control of imatinib (ischemic cardiovascular events of all grades: 46/279 patients treated with nilotinib 300 mg BID vs. 10/280 patients treated with imatinib 400 mg QD, 12/258 patients treated with dasatinib 100 mg QD vs. 6/258 patients treated with imatinib 400 mg QD) [1, 2]. In the BFRORE trial, which has followed patients for relatively short periods, the frequency of cardiovascular adverse reactions at 14 months was comparable between bosutinib and the control of imatinib (14/268 patients treated with bosutinib 400 mg QD vs. 14/268 patients treated with imatinib 400 mg QD) [3]. The EPIC trial, which compared the third-generation TKI ponatinib against imatinib, was terminated early after 14 months due to a high incidence of cardiovascular adverse reactions. Serious arterial occlusive events were reported in 10 of 154 patients (6%) treated with ponatinib and 1 of 152 (1%) treated with imatinib in the trial [4].

These events are dose-dependent, but the exact mechanism of onset (e.g., off-target effects) is unknown, and thus it is unclear how to prevent them besides discontinuing TKIs. However, it is at least known that cardiovascular events are significantly more common in patients with comorbidities that contribute to those events (diabetes, hypertension, and dyslipidemia) [5]. Consequently, blood glucose and blood pressure should be strictly controlled, LDL cholesterol should be controlled with a strong statin, and smokers should be instructed to quit smoking [6].

Results of a long-term observational study (NIPPON DATA 80 study) showed that age, sex, blood pressure, lipid levels, diabetes, and smoking history were risk factors for cardiovascular mortality [7]. Before treatment with TKIs, the patient's risk for cardiovascular events should be evaluated with reference to these data. If the patient is high-risk (due to smoking with diabetes and/or dyslipidemia or old age), they should be fully informed of the risks and benefits of second-generation TKIs before consent to treatment is obtained. Periodic monitoring for atherosclerosis by simple noninvasive ankle brachial index assessment or carotid ultrasound is also recommended before and during treatment. It is currently unclear whether antiplatelet drugs are effective for primary prevention of TKI-related arterial occlusive events. However, preventive measures can be considered for patients who are at high risk for cardiovascular events or already have obvious atherosclerosis before TKI therapy.

Though rare, PAH has been reported with dasatinib in addition to ischemic heart disease [8]. PAH was reported in 6 of 258 patients treated with dasatinib and 0 of 258 patients treated with imatinib as of the 5-year mark in the DASISION trial [2]. As it is not possible to predict which patients are at high risk of developing PAH during treatment with dasatinib, monitoring for PAH periodically is recommended for all patients. Periodic BNP testing and Doppler ultrasound are useful in screening and monitoring for PAH [8]. PAH is treated by discontinuation of dasatinib, and has even been shown to be reversible if treated early [9].

The incidence of CKD among patients who received imatinib, nilotinib, or dasatinib as first-line TKI therapy was 58 of 468 (14%), and 49 of those 58 patients (84%) had received imatinib ($p < 0.001$). Other factors associated with CKD besides imatinib were age, history of hypertension, and diabetes. Imatinib was shown to decrease GFR over time in patients without CKD at baseline [10]. Consequently, attention must also be paid to CKD during long-term TKI therapy.

References

1. Kantarjian HM, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021; 35(2): 440–53. **(1iiDiv)**

2. Cortes JE, et al. Final 5-Year Study Results of DASISION: The Dasatinib Versus Imatinib Study in Treatment-Naïve Chronic Myeloid Leukemia Patients Trial. J Clin Oncol. 2016; 34(20): 2333–40. **(1iiDiv)**

3. Cortes JE, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018; 36(3): 231–7. **(1iiDiv)**

4. Lipton JH, et al. Ponatinib versus imatinib for newly diagnosed chronic myeloid leukaemia: an international, randomised, open-label, phase 3 trial. Lancet Oncol. 2016; 17(5): 612–21. **(1iiDiv)**

5. Rea D, et al. Usefulness of the 2012 European CVD risk assessment model to identify patients at high risk of cardiovascular events during nilotinib therapy in chronic myeloid leukemia. Leukemia. 2015; 29(5): 1206–9. **(Review)**

6. Valent P, et al. Vascular safety iss es in CML patients treated with BCR/ABL1 kinase inhibitors. Blood. 2015; 125(6): 901–6. **(Review)**

7. NIPPON DATA80 Research Group. Risk assessment chart for death from cardiovascular disease based on a 19-year follow-up study of a Japanese representative population. Circ J. 2006; 70(10): 1249–55. **(3iA)**

8. Montani D, et al. Pulmonary arterial hypertension in patients treated by dasatinib. Circulation. 2012; 125(17): 2128–37. **(3iC)**

9. Shah NP, et al. Clinical features of pulmonary arterial hypertension in patients receiving dasatinib. Am J Hematol. 2015; 90(11): 1060–4. **(3iiiDiv)**

10. Yilmaz M, et al. Estimated glomerular filtration rate changes in patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. Cancer. 2015; 121(21): 3894–904. **(3iiiDiv)**

CQ 5 At what time during CML treatment should allo-HSCT be considered?

Recommendation grade: Category 2A
• For newly diagnosed CML-BP patients and CML-AP/BP patients on TKI therapy, allo-HSCT should be performed after treatment with a TKI or additional drugs aiming to achieve reversion to the chronic phase.
• In newly diagnosed CML-AP patients, treatment with a second-generation TKI should be attempted first. If the response to TKI therapy is inadequate, treatment with a TKI not previously used is recommended. If the response remains inadequate, preparations for allo-HSCT should be made. • Allo-HSCT should be considered for CML-CP patients resistant or intolerant to multiple TKIs and asciminib.

Explanation

Allo-HSCT is the only curative treatment option for CML, and until 2002, all CML patients with a suitable HLA-matched donor were candidates for allo-HSCT. Although allo-HSCT is rarely chosen as first-line therapy for CML-CP today given the remarkable improvements in prognosis for CML brought about by TKIs and the availability of multiple selective TKIs, [1, 2] allo-HSCT remains an important treatment option for CML-AP/BP.

For newly diagnosed CML-BP patients and CML-AP/BP patients on TKI therapy, allo-HSCT should be performed after treatment with a TKI or additional drugs aiming to achieve reversion to the chronic phase. In AP/BP patients, treatment should be approached with allo-HSCT in mind right from the beginning, and a donor search performed, because the duration of CP reversion is often short [3]. For CML-BP in particular, a TKI should be selected based on sensitivity, and combination with chemotherapy can be expected to improve response [4]. An ALL-style chemotherapy regimen that includes vincristine and a steroid is used for lymphoid BP, [5] whereas an AML-style regimen that includes cytarabine is used for myeloid BP [6]. The long-term survival rate of CML-AP/BP patients who achieve a second CP and undergo myeloablative allo-HSCT is approximately 30% to 40% [7]. Survival rates in a Japanese study of allo-HSCT for CML-BP were 46.2% with a related donor and 43.9% with an unrelated donor at 1 year after HSCT, and 24.6% and 24.1% respectively at 5 years after HSCT [8].

Although no prospective randomized controlled trials (RCTs) have evaluated TKI therapy in newly diagnosed CML-AP, it is considered advisable to use second-generation TKIs from the beginning due to their greater efficacy [9]. Approximately 20% to 40% of AP patients achieve CCyR with a TKI alone, but the response is often not durable. In contrast, favorable 5-year PFS rates of 50% to 80% have been reported for allo-HSCT recipients [10]. Low-risk CML-AP patients without risk factors such as ≥ 12 months elapsed since CML diagnosis, hemoglobin ≤ 10 g/dL, or peripheral blasts $\geq 5\%$ do not require urgent allo-HSCT. In one study, allo-HSCT improved prognosis in patients with any one of these risk factors, and treatment with TKI alone resulted in a particularly poor prognosis in patients with two or more risk factors [10].

Allo-HSCT remains indicated for CML-CP resistant or intolerant to TKIs. Patients who fail treatment with second-line TKIs can achieve CCyR after third-line treatment with a TKI, particularly if the reason for switching is resistance rather than intolerance to the previous TKI, but the response rate is variable and the duration of response less certain [11]. Therefore, allo-HSCT must be considered for all CML-CP patients who do not achieve sustained CCyR after treatment with two or more TKIs or asciminib.

The T315I gatekeeper mutation is detected in approximately 20% of patients who do not achieve sustained CCyR after first-line TKI therapy. These patients were once included in the indications for HSCT, but the indication was later changed with the approval of ponatinib, which is also effective against T315I [12]. However, preparations for allo-HSCT should be made if a patient with T315I mutation shows early or acquired resistance to ponatinib and HSCT is feasible [13].

Although rare, severe thrombocytopenia may occur in TKI-treated patients despite appropriate TKI dose reduction and supportive measures such as cytokine therapy. This may lead to frequent treatment interruptions, preventing effective and sustained TKI therapy. These patients are likely to have insufficient remaining normal hematopoietic function to repopulate the bone marrow, so allo-HSCT is the only

effective treatment that can provide excellent long-term survival rate in this group.

The decision of whether to perform allo-HSCT for CML-CP is particularly challenging, but some studies suggest that delayed HSCT is not always associated with a worse prognosis [10, 14].

References

1. Baccarani M, et al.; European LeukemiaNet. Chronic myeloid leukemia: an update of concepts and management recommendations of European LeukemiaNet. J Clin Oncol. 2009; 27(35): 6041–51. **(Review)**

2. Jabbour E, et al. Chronic myeloid leukemia: 2012 update on diagnosis, monitoring, and management. Am J Hematol. 2012; 87(11): 1037–45. **(Review)**

3. Hehlmann R, et al. Management of CML-blast crisis. Best Pract Res Clin Haematol. 2016; 29(3): 295–307. **(Review)**

4. Jain P, et al. Prognostic factors and survival outcomes in patients with chronic myeloid leukemia in blast phase in the tyrosine kinase inhibitor era: Cohort study of 477 patients. Cancer. 2017; 123(22): 4391–402. **(3iiiDiv)**

5. Yanada M, et al. High complete remission rate and promising outcome by combination of imatinib and chemotherapy for newly diagnosed BCR-ABL-positive acute lymphoblastic leukemia: a phase II study by the Japan Adult Leukemia Study Group. J Clin Oncol. 2006; 24(3): 460–6. **(3iiiDiv)**

6. Fruehauf S, et al. Imatinib combined with mitoxantrone/etoposide and cytarabine is an effective induction therapy for patients with chronic myeloid leukemia in myeloid blast crisis. Cancer. 2007; 109(8): 1543–49 **(3iiiDiv)**

7. Crawley C, et al.; Chronic Leukemia Working Party of the EBMT. Outcomes of reduced-intensity transplantation for chronic myeloid leukemia: an analysis of prognostic factors from the Chronic Leukemia Working Party of the EBMT. Blood. 2005; 106(9): 2969–76. **(3iiiA)**

8. Hematopoietic Cell Transplantation in Japan: Annual Report of Nationwide Survey 2013. Japanese Data Center for Hematopoietic Cell Transplantation/Japan Society for Hematopoietic Stem Cell Transplantation. http://www.jdchct.or.jp/data/report/2013/3-3-4.pdf **(Review)**

9. Ohanian M, et al. Tyrosine kinase inhibitors as initial therapy for patients with chronic myeloid leukemia in accelerated phase. Clin Lymphoma Myeloma Leuk. 2014, 14(2): 155–62.e1. **(3iiiA)**

10. Jiang Q, et al. Imatinib mesylate versus allogeneic hematopoietic stem cell transplantation for patients with chronic myelogenous leukemia in the accelerated phase. Blood. 2011; 117(11): 3032–40. **(3iiiDiv)**

11. Khoury HJ, et al. Bosutinib is active in chronic phase chronic myeloid leukemia after imatinib and dasatinib and/or nilotinib therapy failure. Blood. 2012; 119(15): 3403–12. **(2iiiDiv)**

12. Cortes JE, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018; 132(4): 393–404. **(3iiiDiv)**

13. Nicolini FE, et al. Overall survival with ponatinib versus allogeneic stem cell transplantation in Philadelphia chromosome-positive leukemias with the T315I mutation. Cancer. 2017; 123(15): 2875–80. **(3iA)**

14. Hehlmann R, et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood. 2007; 109(11): 4686–92. **(2A)**

CQ 6 Is it recommended to discontinue TKIs after achieving DMR if minimal residual disease (MRD) is not detected?

Recommendation grade: Category 2A
Discontinuation of TKIs can be considered for patients who face obstacles to continuing TKIs such as trying to become pregnant or experiencing late adverse reactions, as well as patients who have achieved DMR and meet certain criteria, as long as they are monitored periodically. If discontinuation is attempted outside of a clinical trial, registration in the Japanese Society of Hematology (JSH) J-SKI registry by a hematologist is recommended.

Explanation

TFR is the new goal of CML-CP treatment. About half of patients diagnosed with CML-CP who maintained DMR for a certain period (≥ 1–2 years) after first-line therapy with imatinib (STIM trial, JALSG STIM213 trial) [1, 2], nilotinib (ENESTfreedom trial, JALSG N-STOP trial) [3, 4], or dasatinib (first-line DADI trial, JALSG D-STOP trial) [5, 6] were able to maintain TFR without molecular relapse after TKI discontinuation. Moreover, about half of patients who were resistant or intolerant to the first-line TKI but were able to maintain DMR for a certain period after second-line therapy with nilotinib (ENESTop trial) [7] or dasatinib (DADI trial) [8] were able to maintain TFR even after TKI discontinuation. It should be noted that the TFR rate is very low in patients who switch TKIs

due to previous TKI resistance, so TKIs should not be discontinued in such patients at this time.

TFR is undoubtedly a goal of CML-CP treatment because it reduces health economical costs and avoids overtreatment and late toxicity associated with long-term treatment. In Europe and the United States, EURO-SKI and other large clinical trials have established criteria for safe completion of TKI therapy, and specialists discontinue TKI therapy in routine practice. It is particularly appropriate to consider discontinuation of TKI in special circumstances (e.g., when the patient is trying to become pregnant or is experiencing a serious adverse reaction) provided that strict MRD monitoring by quantitative PCR is performed. TKI discontinuation trials conducted in Japan to date (e.g., JALSG STIM213, DADI, 1st DADI, NIL-Stop, STAT2, JALSG N-STOP, JALSG D-STOP) have further verified the feasibility of TKI discontinuation, and have not observed stage progression. Therefore, the JSH launched a new registry study called "Multi-Institutional Collaborative Study for Estimating the Persistence of Treatment Free Remission in Chronic Myeloid Leukemia after Stopping Tyrosine Kinase Inhibitor in Japan" (J-SKI) [9]. It is acceptable for a hematologist to attempt TKI discontinuation by enrolling the patient in the J-SKI registry.

The NCCN guidelines list the following as conditions that must be met to attempt TKI discontinuation outside of a clinical trial [10].

(1) Age ≥ 18 years.
(2) CML-CP with no history of CML-AP/BP.
(3) On TKI therapy for ≥ 3 years.
(4) Stable $MR^{4.0}$ for at least 2 years with testing ≥ 4 times at intervals of ≥ 3 months.
(5) Access to a reliable test that can detect $MR^{4.5}$ with results available within 2 weeks.
(6) *BCR::ABL1* mRNA (IS) can be measured monthly for the first 6 months after discontinuation, once every 2 months at 7–12 months, and every 3 months thereafter for patients maintaining MMR.
(7) In patients who resume TKI therapy after loss of MMR, *BCR::ABL1* mRNA (IS) can be measured monthly until second MMR is confirmed, and every 3 months thereafter In patients who do not achieve MMR at 3 months after TKI resumption, *BCR::ABL1* kinase domain mutation testing should be performed and monthly *BCR::ABL1* mRNA (IS) monitoring must be continued for an additional 6 months.

Withdrawal syndrome, mainly presenting as musculoskeletal pain, may occur in 20% to 30% of patients after TKI discontinuation, although the pathogenic mechanism is unknown, so informed consent must be obtained before discontinuation. Withdrawal syndrome is transient and often resolves with symptomatic treatment [11].

Research has shown that a second attempt at TKI discontinuation is possible in patients who were unable to maintain TFR after the first attempt but maintained DMR for a certain period of time after TKI resumption. The TFR rate at 24 months after the second TKI discontinuation attempt was higher in patients who had maintained DMR for the first 3 months after the first attempt than in other patients (72% vs. 36%) [12]. At present, little data exists regarding second attempts at TKI discontinuation, so this generally should only be done in a clinical trial. Lifelong MRD monitoring during TFR is required at this time because no data from long-term observation (≥ 10 years) are available and late molecular relapse cannot be completely ruled out.

References

1. Mahon FX, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol. 2010; 11(11): 1029–35. **(3iiiDiv)**

2. Takahashi N, et al. Deeper molecular response is a predictive factor for treatment-free remission after imatinib discontinuation in patients with chronic phase chronic myeloid leukemia: the JALSG-STIM213 study. Int J Hematol. 2018 Feb; 107(2): 185–93. **(3iiiDiv)**

3. Hochhaus A, et al. Treatment-free remission following frontline nilotinib in patients with chronic myeloid leukemia in chronic phase: results from the ENESTfreedom study. Leukemia. 2017; 31(7): 1525–31. **(3iiiDiv)**

4. Takahashi N, et al. Treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline nilotinib: results from JALSG N-STOP216. EHA Library. 2021: 325,427; EP667. **(3iiiDiv)**

5. Kimura S, et al. Treatment-free remission after first-line dasatinib discontinuation in patients with chronic myeloid leukaemia (first-line DADI trial): a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2020; 7(3): e218-25. **(3iiiCiv)**

6. Minami Y, et al. Treatment-free remission in patients with chronic myeloid leukemia in chronic phase following frontline dasatinib: results from JALSG D-STOP216. EHA Library. 2021: 325,428; EP668. **(3iiiDiv)**

7. Hughes TP, et al. Long-term treatment-free remission in patients with chronic myeloid leukemia after second-line nilotinib: ENESTop 5-year update. Leukemia. 2021;35(6): 1631–42. **(3iiiCiv)**

8. Imagawa J, et al. Discontinuation of dasatinib in patients with chronic myeloid leukaemia who have maintained deep molecular response for longer than 1 year(DADI trial): a

multicentre phase 2 trial. Lancet Haematol. 2015;2(12): e528-35. **(3iiiDiv)**

9. Multi-Institutional Collaborative Study for Estimating the Persistence of Treatment Free Remission in Chronic Myeloid Leukemia after Stopping Tyrosine Kinase Inhibitor in Japan: J-SKI (Japan Stop TKI study). http://www.jshem.or.jp/uploads/files/research/JSH-J-SKI_Protocol_190805.pdf

10. Deininger MW, et al. Chronic Myeloid Leukemia, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw. 2020; 18(10): 1385–415. **(Review)**

11. Lee SE, et al. Imatinib withdrawal syndrome and longer duration of imatinib have a close association with a lower molecular relapse after treatment discontinuation: the KID study. Haematologica. 2016; 101(6): 717–23. **(3iiiCiv)**

12. Legros L, et al. Second tyrosine kinase inhibitor discontinuation attempt in patients with chronic myeloid leukemia. Cancer. 2017; 123(22): 4403–10. **(3iiiCiv)**

CQ 7 Is TKI dose reduction during TKI therapy for CML recommended?

Recommendation grade: Category 1 TKI doses must be adjusted in accordance with dose reduction criteria for TKI-related adverse events. The dose of ponatinib must be reduced to 15 mg while monitoring response to treatment (targeting IS ≤ 1%) to ensure long-term safety.
Recommendation grade: Category 2A TKI doses can be reduced to avoid adverse events in elderly patients and other patients at high risk.
Recommendation grade: Category 2B In patients maintaining DMR, TKI doses may be reduced to avoid TKI-related adverse events.

Explanation

Dose adjustment based on TKI dose reduction criteria

Standard doses of TKIs (imatinib 400 mg QD, bosutinib 400 mg QD, dasatinib 100 mg QD, and nilotinib 300 mg BID) have been established through clinical trials (IRIS, [1] BFORE, [2] DASISION, [3] and ENESTnd [4]) conducted to develop TKIs for newly diagnosed CML-CP, but TKI doses must be adjusted in accordance with dose reduction criteria for TKI-related adverse events. The package inserts state that the dosage and administration should be reduced as appropriate based on the patient's condition, and list criteria for treatment interruption and dose reduction based on adverse event severity.

The standard dose of ponatinib for CML was established as 45 mg QD in the PACE trial [5] started in 2010, and ponatinib was approved for treatment-resistant CML with the T315I mutation in the United States in 2012, Europe in 2013, and Japan in 2016. However, unexpected vaso-occlusive events were reported in high cardiovascular risk patients and adverse events were presumed to be dose-dependent, so beginning in 2013, the recommendation became to reduce the dose to 15 mg in patients who achieve MCyR and to 30 mg in patients who do not achieve MCyR or who are progressing to AP. In Japan, the dosage for first-line ponatinib is 45 mg QD, but in consideration of the risks and benefits, Japanese clinicians have taken the approach of starting at a dosage of 15 mg or 30 mg QD, which has ensured safe use. An RCT (OPTIC trial) [6] that compared initial ponatinib doses of 15 mg, 30 mg, and 45 mg for CML resistant to prior therapy showed that 15- and 30-mg doses can have adequate efficacy in patients without the T315I mutation and with little TKI resistance, while reducing the incidence of vaso-occlusive events. The dose of ponatinib must be reduced to 15 mg while monitoring response to treatment (targeting IS ≤ 1%) to ensure long-term safety.

TKI dose reduction for elderly patients and high-risk patients

The OPTIC trial [6] discussed above was the first large RCT to determine dose adjustment strategies for a TKI and may provide evidence for considering similar strategies for other TKIs. Although limited evidence exists to support a strategy of starting TKI therapy (with imatinib, bosutinib, dasatinib, or nilotinib) at a reduced dose, it may be useful in patients at high risk of TKI-related adverse events and elderly patients.

The standard dose of imatinib for newly diagnosed CML in the IRIS trial was 400 mg QD, [1] but a Japanese prospective study in newly diagnosed CML (JALSG CML202) showed similar efficacy at 300 mg QD [7]. In the JALSG CML202 trial, trough levels of imatinib did not differ significantly between the 300 mg and 400 mg groups [7]. Although imatinib blood levels are dose-dependent, the Japanese population has unique single nucleotide polymorphisms in drug transporters such as ABCG2, which causes large individual variation in the distribution of blood levels [8]. As the proportion of patients reaching the target imatinib blood level of 1000 ng/mL or higher is significantly greater among patients who have achieved MMR compared with those who have not achieved MMR,

blood level monitoring is also useful to confirm adherence in patients who have not achieved MMR [9].

The standard dose of bosutinib for newly diagnosed CML is 400 mg QD based on the BFORE trial, [2] but CML specialists in Japan start with 200 mg QD and titrate up to 400 mg in many cases [10]. Besides providing supportive care for diarrhea and other gastrointestinal problems, it is also possible to take early measures against liver injury, which is common in Japanese patients. However, if bosutinib is well tolerated, it is important to increase the dose up to the standard dose. Clinical trials in the development stage have allowed for dose reduction to a minimum of 300 mg QD, but there is no evidence of long-term efficacy at doses lower than this. A prospective clinical trial to validate the bosutinib dose titration approach for CML is currently underway in Japan.

The standard dose of dasatinib for newly diagnosed CML is 100 mg QD based on the DASISION trial [3]. However, studies in small, limited cohorts showed that 50 mg QD can have similar efficacy, while avoiding adverse events such as pleural effusion and cytopenia [11–13]. It may be necessary to start treatment at a low dose in elderly patients considered to be at particularly high risk of adverse events. However, there is no evidence for low-dose dasatinib in high-risk patients. When treating younger patients, it is also important to note that low-dose dasatinib may affect the likelihood of achieving TFR after DMR.

The standard dose of nilotinib for newly diagnosed CML is 300 mg BID based on the ENESTnd trial [4]. Over the long 10-year observation period in the ENESTnd trial, [14] the incidence of vaso-occlusive events was lower at 300 mg BID than at 400 mg BID, indicating that vaso-occlusive event incidence may be dose-dependent as it is with ponatinib. A study in a small, limited cohort demonstrated the usefulness and safety of 300 mg BID versus 400 mg BID in second-line therapy as well [15]. Clinical trials in the development stage allowed for dose reduction to a minimum of 400 mg QD, but there is no evidence of efficacy at doses lower than this.

TKI dose reduction for patients maintaining DMR

TKI dose reduction to avoid late TKI-related adverse events may be considered for CML patients who have been on TKI therapy long-term (≥ 3 years) and have maintained DMR (IS $\leq 0.0032\%$) for at least 12 months. Regular IS monitoring after dose reduction is necessary to ensure the maintenance of deep response. A study where a mathematical model was created using data from independent clinical trials concluded that a 50% TKI dose reduction does not result in loss of long-term efficacy in patients who have already been maintaining deep response [16].

References

1. O'Brien SG, et al. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003; 348(11): 994–1004. **(1iiDiv)**

2. Cortes JE, et al. Bosutinib Versus Imatinib for Newly Diagnosed Chronic Myeloid Leukemia: Results From the Randomized BFORE Trial. J Clin Oncol. 2018; 36(3): 231–7. **(1iiDiv)**

3. Kantarjian HM, et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012; 119(5): 1123–9. **(1iiDiv)**

4. Kantarjian HM, et al. Nilotinib versus imatinib for the treatment of patients with newly diagnosed chronic phase, Philadelphia chromosome-positive, chronic myeloid leukaemia: 24-month minimum follow-up of the phase 3 randomised ENESTnd trial. Lancet Oncol. 2011; 12(9): 841–51. **(1iiDiv)**

5. Cortes JE, et al. Ponatinib efficacy and safety in Philadelphia chromosome-positive leukemia: final 5-year results of the phase 2 PACE trial. Blood. 2018; 132(4): 393–404. **(3iiiDiv)**

6. Cortes J, et al. Ponatinib dose-ranging study in chronic-phase chronic myeloid leukemia: a randomized, open-label phase 2 clinical trial. Blood. 2021; 138(21): 2042–50. **(1iiDiv)**

7. Ohnishi K, et al. Long-term outcome following imatinib therapy for chronic myelogenous leukemia, with assessment of dosage and blood levels: the JALSG CML202 study. Cancer Sci. 2012; 103(6): 1071–8. **(2Div)**

8. Takahashi N, et al. Influence of CYP3A5 and drug transporter polymorphisms on imatinib trough concentration and clinical response among patients with chronic phase chronic myeloid leukemia. J Hum Genet. 2010; 55(11): 731–7. **(3iiDiv)**

9. Takahashi N, et al. Correlation between imatinib pharmacokinetics and clinical response in Japanese patients with chronic-phase chronic myeloid leukemia. Clin Pharmacol Ther. 2010; 88(6): 809–13. **(3iiDiv)**

10. Mita A, et al. Correlation of plasma concentration and adverse effects of bosutinib: standard dose or doseescalation regimens of bosutinib treatment for patients with chronic myeloid leukemia. Exp Hematol Oncol. 2018; 7: 9. **(3iiDiv)**

11. Naqvi K, et al. Early results of lower dose dasatinib (50 mg daily) as frontline therapy for newly diagnosed chronic-phase chronic myeloid leukemia. Cancer. 2018; 124(13): 2740–7. **(2Div)**

12. Naqvi K, et al. Long-term follow-up of lower dose dasatinib (50 mg daily) as frontline therapy in newly diagnosed

chronic-phase chronic myeloid leukemia. Cancer. 2020; 126(1): 67–75. **(2Div)**

13. Murai K, et al. Low-dose dasatinib in older patients with chronic myeloid leukaemia in chronic phase (DAVLEC): a single-arm, multicentre, phase 2 trial. Lancet Haematol. 2021; 8(12): e902-11. **(2Div)**

14. Kantarjian HM, et al. Long-term outcomes with frontline nilotinib versus imatinib in newly diagnosed chronic myeloid leukemia in chronic phase: ENESTnd 10-year analysis. Leukemia. 2021; 35(2): 440–53. **(1iiDiv)**

15. Hiwase D, et al. Efficacy and safety of nilotinib 300 mg twice daily in patients with chronic myeloid leukemia in chronic phase who are intolerant to prior tyrosine kinase inhibitors: Results from the Phase IIIb ENESTswift study. Leuk Res. 2018; 67: 109–15. **(2Div)**

16. Fassoni AC, et al. Reduced tyrosine kinase inhibitor dose is predicted to be as effective as standard dose in chronic myeloid leukemia: a simulation study based on phase III trial data. Haematologica. 2018; 103(11): 1825–34. **(1iiDiv)**

CQ 8 What is the recommended approach to management of pregnancy in a CML patient or patient's partner?

> Recommendation grade: Category 2B
> TKI therapy is not recommended for female CML patients who are pregnant or breastfeeding. Treatment with IFN-α or discontinuation of TKI therapy is recommended during pregnancy. There is no need to recommend TKI discontinuation for male patients.

Explanation

When a patient or patient's partner is trying to conceive, they should be informed that these guidelines are based on empirical evidence, and the treatment plan should be determined carefully with consideration to the patient's wishes and to risks.

When a CML patient on TKI therapy or their partner is trying to conceive

It is not necessary to discontinue treatment with imatinib or a second-generation TKI (including dasatinib, nilotinib, and bosutinib) in male patients trying to conceive with their partner. Several studies have shown that children of male patients who receive these treatments do not have a higher rate of congenital anomalies [1–3]. However, the teratogenicity of ponatinib and asciminib to children of male patients is unknown [3]. Although the effects of TKIs on fertility have not been fully investigated, one study showed no changes in sperm quality or morphology after treatment with imatinib [3]. Sperm preservation before TKI therapy is an option, but no data exist on sperm quality in untreated male CML patients. The general risk of teratogenicity should be thoroughly discussed and the patient's wishes considered, but there is no need to discontinue TKI therapy.

However, discontinuation of TKI therapy or switching to another treatment should be proactively considered for female patients trying to conceive [3]. This is because TKIs transfer into the placenta and the fetus, increasing risks of both miscarriage and fetal anomalies [1–5]. Because patients who have achieved and maintained deep response have a good chance of achieving TFR, it is feasible to discontinue TKI therapy before the patient starts trying to conceive (see CQ6) [3]. Therefore, the feasibility of TKI discontinuation should be considered carefully on a patient-by-patient basis while reviewing past treatment history and response. Patients who are not suitable candidates for TKI discontinuation or who relapse after discontinuation are switched to INF-α [3, 6]. However, because non-TKI therapy risks disease progression, this decision should be made upon thorough discussion with the patient, with consideration to their condition and their wishes. Ideally, female patients should delay pregnancy until after a 6-month TFR monitoring period, when the risk of relapse after TKI discontinuation is lower [7]. If the patient becomes pregnant, close collaboration with an obstetrician specializing in high-risk pregnancies and periodic fetal ultrasounds are recommended [3]. In addition, breastfeeding is contraindicated during TKI therapy because TKIs transfer into breast milk [3, 8]. If a patient wishes to breastfeed, TKI therapy should be discontinued to avoid TKI exposure to the child [3, 8]. Pharmacokinetic studies of TKIs indicate that elimination of TKIs from the body takes at least a few days after TKI discontinuation [9].

When a CML patient on TKI therapy or their partner becomes pregnant

When a patient experiences an unexpected pregnancy during TKI therapy for CML, it is necessary to discuss the options for TKI therapy (whether to continue, discontinue, or change to another treatment) and the pregnancy (whether or not to continue) with the patient and make decisions in accordance with that patient's wishes. TKIs are teratogenic due to off-target effects, so TKI exposure during pregnancy must be avoided,

especially during organogenesis [1–4]. Therefore, if pregnancy is suspected during CML treatment, TKIs should be stopped immediately and the patient should be tested to confirm pregnancy. Once a normal pregnancy is confirmed, the TKI is switched to IFN-α [3, 6]. However, in patients expected to maintain TFR, it is also an option to discontinue TKI therapy without switching to any other treatment upon confirmation of pregnant, as long as the patient is strictly monitored (see CQ6) [3]. Although some studies suggest that imatinib can be used safely in the second (16–27 weeks) and third (28–39 weeks) trimesters, it is not recommended at this time due to a lack of case data [3, 4]. Other TKIs besides imatinib are similarly not recommended [1–4]. For patients who have advanced CML or are refractory to IFN-α, the decision to use a TKI in the second or third trimester of pregnancy or terminate the pregnancy before 22 weeks should be made carefully and in accordance with the patient's wishes after explaining the risks and benefits. Whichever decision is made, the patient's care should be managed in close coordination with an obstetrician specialized in high-risk pregnancies.

When CML was diagnosed during pregnancy

IFN-α is used for first-line treatment of CML in female patients diagnosed during pregnancy [3, 6]. Hydroxyurea and TKIs are not recommended. Leukapheresis for patients with marked leukocytosis is also an option during pregnancy [3]. Close observation can be another option for patients with mild leukocytosis, who may be able to delay treatment until after delivery [3]. For patients who have advanced CML or are refractory to IFN-α, the decision to use a TKI in the second or third trimester of pregnancy or terminate the pregnancy before 22 weeks should be made carefully and in accordance with the patient's wishes after explaining the risks and benefits. Whichever decision is made, the patient's care should be managed in close coordination with an obstetrician specialized in high-risk pregnancies.

References

1. Cortes JE, et al. The impact of dasatinib on pregnancy outcomes. Am J Hematol. 2015; 90(12): 1111–5. **(3iiiC)**

2. Cortes JE, et al. Pregnancy outcomes in patients treated with bosutinib. Int J Hematol Oncol. 2020; 9(2): IJH26. **(3iiiC)**

3. Hochhaus A, et al. European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia. Leukemia. 2020; 34(4): 966–84. **(Review)**

4. Pye SM, et al. The effects of imatinib on pregnancy outcome. Blood. 2008; 111(12): 5505–8. **(3iiiC)**

5. Chelysheva E, et al. Placental transfer of tyrosine kinase inhibitors used for chronic myeloid leukemia treatment. Leuk Lymphoma. 2018; 59(3): 733–8. **(3iiiC)**

6. Lasica M, et al. The effect of tyrosine kinase inhibitor interruption and interferon use on pregnancy outcomes and long-term disease control in chronic myeloid leukemia. Leuk Lymphoma. 2019; 60(7): 1796–802. **(3iiiC)**

7. Abruzzese E, et al. Tyrosine kinase inhibitors and pregnancy in chronic myeloid leukemia: opinion, evidence, and recommendations. Ther Adv Hematol. 2020; 11: 2,040,620,720,966,120. **(Review)**

8. Chelysheva E, et al. Breastfeeding in Patients with Chronic Myeloid Leukaemia: Case Series with Measurements of Drug Concentrations in Maternal Milk and Literature Review. Mediterr J Hematol Infect Dis. 2018; 10(1): e2018027. **(3iiiC)**

9. Apperley J. CML in pregnancy and childhood. Best Pract Res Clin Haematol. 2009; 22(3): 455–74. **(Review)**

CQ 9 Is aspirin recommended for all patients with PV/ET/MF?

Recommendation grade: Category 1 Aspirin is recommended for all patients with PV unless contraindicated.
Recommendation grade: Category 2A For ET, aspirin may be useful for patients with thrombotic risk or *JAK2*V617F mutation, rather than for all patients.
Recommendation grade: Category 2B For MF, aspirin can be considered for patients with a history of thrombosis or cardiovascular risk.

Explanation

For PV, a prospective RCT validated the benefit of aspirin for prevention of thrombotic and hemorrhagic complications [1]. The trial excluded patients with contraindications to aspirin and patients with clear indication for aspirin treatment (e.g., a history of thrombosis), but set no age restrictions. In other words, aspirin is indicated for low-risk and some high-risk patients under the current criteria. Aspirin significantly reduced the combined incidence of nonfatal myocardial infarction, nonfatal stroke, death from cardiovascular causes, pulmonary embolism, and major venous thrombosis compared with placebo (relative risk [RR] 0.4, $p = 0.03$). Rates of hemorrhagic complications did not differ

between groups. A prospective cohort study also showed that use of antiplatelet drugs reduces cardiovascular events (RR 0.77) and mortality (RR 0.72) [2]. This study included all patients with PV regardless of age or history of thrombosis. Based on evidence from these two clinical trials, aspirin is recommended in all patients with PV, regardless of age or history of thrombosis.

For ET, the thromboprophylactic effect of antiplatelet therapy has only been investigated in retrospective observational studies. An analysis of low-risk ET patients showed that antiplatelet therapy reduced the risk of venous thrombosis in patients with the *JAK2* V617F mutation and the risk of arterial thrombosis in patients with cardiovascular risk [3]. On the other hand, antiplatelet therapy increased the risk of hemorrhage in patients with platelet counts higher than 1,000,000/μL. A retrospective observational study where low-risk ET patients were stratified based on driver mutations has been reported [4]. Antiplatelet therapy did not reduce the risk of thrombosis and actually increased the risk of hemorrhage in patients with *CALR* mutations. However, aspirin reduced the risk of venous thrombosis in patients with the *JAK2* V617F mutation [4]. Therefore, universal aspirin administration is not recommended for low-risk ET; rather, the need for aspirin should be determined based on the type of driver mutation, cardiovascular risk status, and platelet count. Yet another retrospective observational study investigated the significance of adding antiplatelet therapy to cytoreductive therapy in high-risk ET patients (e.g., ≥ 60 years or severe thrombocytosis) without a history of thrombosis [5]. This study showed that addition of antiplatelet therapy reduced the risk of thrombosis in patients aged 60 years and older (incidence RR 0.2, $p = 0.02$) [5]. Furthermore, a retrospective observational study of recurrent thrombosis in PV and ET patients with a history of thrombosis demonstrated the efficacy of anticoagulant or antiplatelet therapy for reducing venous and arterial thrombosis when added to cytoreductive therapy [6]. On the basis of these results, addition of antiplatelet therapy to cytoreductive therapy is recommended for high-risk ET.

Thrombotic risk in PMF, particularly pre-PMF, is comparable to that in ET [7]. It has also been noted that patients with pre-PMF are more prone to hemorrhage than those with ET [8]. However, no clinical studies have validated whether aspirin reduces the risk of thrombosis in patients with PMF. According to expert opinion, aspirin should be considered in patients who is older than 60 years or cardiovascular risk factors, the *JAK2* V617F mutation, or leukocytosis [9]. Aspirin and anticoagulant therapy are also suggested as options for patients with a history of thrombosis.

Patients will sometimes develop acquired von Willebrand syndrome (AvWS) if their von Willebrand factor (vWF) level decreases due to a marked increase in platelet count (generally to > 1,000,000/μL) [10]. Treatment with aspirin alone can promote hemorrhage in such patients, and thus aspirin should not be started in patients with reduced vWF:RCo (ristocetin cofactor activity) until the platelet count is successfully reduced by cytoreductive therapy. In addition, patients with a platelet count less than 1,000,000/μL can sometimes have a low vWF level as well, and thus testing for vWF:RCo is advisable for all patients with a bleeding tendency regardless of platelet count.

References

1. Landolfi R, et al. Efficacy and safety of low-dose aspirin in polycythemia vera. N Engl J Med. 2004; 350(2): 114–24. **(1iDi)**

2. Marchioli R, et al. Vascular and neoplastic risk in a large cohort of patients with polycythemia vera. J Clin Oncol. 2005; 23(10): 2224–32. **(3iiC/2Di)**

3. Alvarez-Larrán A, et al. Observation versus antiplatelet therapy as primary prophylaxis for thrombosis in low-risk essential thrombocythemia. Blood. 2010; 116(8): 1205–10. **(3iiC)**

4. Alvarez-Larrán A, et al. Antiplatelet therapy versus observation in low-risk essential thrombocythemia with a CALR mutation. Haematologica. 2016; 101(8): 926–31. **(3iiC)**

5. Alvarez-Larrán A, et al. Cytoreduction plus low-dose aspirin versus cytoreduction alone as primary prophylaxis of thrombosis in patients with high-risk essential thrombocythaemia: an observational study. Br J Haematol. 2013; 161(6): 865–71. **(3iiC)**

6. De Stefano V, et al. Recurrent thrombosis in patients with polycythemia vera and essential thrombocythemia: incidence, risk factors, and effect of treatments. Haematologica. 2008; 93(3): 372–80. **(3iiC)**

7. Barbui T, et al. Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. J Clin Oncol. 2011; 29(23): 3179–84. **(3iiC)**

8. Finazzi G, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. Leukemia. 2012; 26(4): 716–9. **(3iiC)**

9. Finazzi G, et al. Prefibrotic myelofibrosis: treatment algorithm 2018. Blood Cancer J. 2018; 8(11): 104. **(Review)**

10. Rottenstreich A, et al. Factors related to the development of acquired von Willebrand syndrome in patients with essential thrombocythemia and polycythemia vera. Eur J Intern Med. 2017; 41: 49–54. **(3iiC)**

CQ 10 Is cytoreductive therapy recommended for low-risk PV/ET patients?

Recommendation grade: PV - Category 3, ET - Category 4
Cytoreductive therapy with cytotoxic drugs to reduce thrombotic risk is not recommended for low-risk PV/ET patients.

Explanation

The ELN and NCCN guidelines also deem cytoreductive therapy to be unnecessary for low-risk PV/ET [1, 2]. However, supporting evidence from clinical trials is minimal.

One clinical trial of cytoreductive therapy for low-risk PV was the Low-PV trial, a randomized, prospective trial of ropeg-IFN-α 2b, which is not covered by Japanese NHI [3]. In this trial, low-risk PV patients were randomized to receive phlebotomy alone or ropeg-IFN-α 2b. The primary endpoint was the percentage of patients maintaining median hematocrit values of lower than 45% without progressive disease during the 12-month observation period. This rate was only 60% with phlebotomy alone versus 84% with ropeg-IFN-α 2b (odds ratio [OR] 3.5). Progression was observed in 4 patients who received phlebotomy alone (3 with thrombocytosis accompanied by erythromelalgia, 1 with splenic vein thrombosis).

In one prospective clinical trial, low-risk ET patients aged 40 to 59 years without hypertension or diabetes requiring therapy or marked thrombocytosis (platelet count ≥ 1,500,000/μL) were randomized to receive aspirin alone or aspirin plus hydroxyurea [4]. The primary endpoint was a composite of arterial or venous thrombosis, hemorrhage, and death from cardiovascular causes. Median follow-up time was 73 months. The hazard ratio for the primary endpoint was exactly the same in both groups, at 0.98. Therefore, the authors concluded that hydroxyurea should not be used in ET patients who meet these conditions [4].

The ELN and NCCN guidelines state that cytoreductive therapy may be indicated even for low-risk PV/ET in patients who are unable to continue phlebotomy due to iron deficiency symptoms or have marked thrombocytosis (platelet count > 1,500,000/μL), leukocytosis (WBC ≥ 15,000/μL), profound general symptoms, or progressive splenomegaly [1, 2]. However, a retrospective analysis by the Mayo Clinic in low-risk ET patients with marked thrombocytosis found that cytoreductive therapy had no effect on thrombosis-free survival rate [5]. No clinical trials have verified the efficacy of cytoreductive therapy for reducing general symptoms in low-risk PV/ET patients.

References

1. Barbui T, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018; 32(5): 1057–69. **(Review)**

2. Mesa RA, et al. NCCN Guidelines Insights: Myeloproliferative Neoplasms, Version 2.2018. J Natl Compr Canc Netw. 2017; 15(10): 1193–207. **(Review)**

3. Barbui T, et al. Ropeginterferon alfa-2b versus phlebotomy in low-risk patients with polycythaemia vera (Low-PV study): a multicentre, randomised phase 2 trial. Lancet Haematol. 2021; 8(3): e175-84. **(1iiC)**

4. Godfrey AL, et al. Hydroxycarbamide Plus Aspirin Versus Aspirin Alone in Patients With Essential Thrombocythemia Age 40 to 59 Years Without High-Risk Features. J Clin Oncol. 2018; 36(34): 3361–9. **(1iiC)**

5. Tefferi A, et al. Extreme thrombocytosis in low-risk essential thrombocythemia: Retrospective review of vascular events and treatment strategies. Am J Hematol. 2021; 96(6): E182-4. **(3iiiC)**

CQ11 Is a hematocrit level of 45% recommended as a treatment target for PV?

Recommendation grade: Category 1
The target should be to control the hematocrit level below 45%.

Explanation

The first study on the relationship between hematocrit level and thrombogenicity in PV, which was published in 1978, showed that maintaining a hematocrit level below 45% reduces the incidence of thrombosis. [1]. Although this was a relatively small (69 patients) retrospective observational study, it has been viewed as a landmark study and has significantly impacted PV treatment practices. Several retrospective cohort studies later attempted to validate the benefit of maintaining a hematocrit level below 45%, but none found supporting results [2, 3]. The concept was finally validated in a prospective clinical trial (CYTO-PV trial) in 2013, in which PV patients were randomly assigned to a hematocrit target below 45% or 45% to 50% [4]. The primary endpoint was time until death from cardiovascular causes or ischemic disorders (stroke, acute coronary syndrome, transient ischemic attack, pulmonary embolism, visceral thrombosis, deep-vein thrombosis, or peripheral arterial

thrombosis). A total of 365 patients were enrolled, and the median follow-up period was 31 months. The hazard ratio for reaching the primary endpoint was significantly higher (HR 3.91, $p=0.004$) when the hematocrit target was 45% to 50% versus below 45%. On the basis of the results from this trial, it is recommended to continue to target a hematocrit level below 45% when treating PV.

References

1. Pearson TC, Wetherley-Mein G. Vascular occlusive episodes and venous haematocrit in primary proliferative polycythaemia. Lancet. 1978; 2(8102): 1219–22. **(3iiiC)**

2. Di Nisio M, et al. The haematocrit and platelet target in polycythemia vera. Br J Haematol. 2007; 136(2): 249–59. **(3iC)**

3. Crisà E, et al. A retrospective study on 226 polycythemia vera patients: impact of median hematocrit value on clinical outcomes and survival improvement with antithrombotic prophylaxis and non-alkylating drugs. Ann Hematol. 2010; 89(7): 691–9. **(3iiA)**

4. Marchioli R, et al. Cardiovascular events and intensity of treatment in polycythemia vera. N Engl J Med. 2013; 368(1): 22–33. **(1iiB)**

CQ12 Is a platelet count of 400,000/μL recommended as a treatment target for ET?

Recommendation grade: Category 2B
The target platelet count in treatment is not clear. A target of 400,000 to 600,000/μL is often used in clinical trials, but there is little evidence for setting a target below 400,000/μL.

Explanation

The ELN response assessment criteria for ET require a platelet count below 400,000/μL as one criterion for complete remission (CR) and partial remission [1]. However, they clearly state that this criterion should only be used for response assessment in clinical trials, and is not intended for use in routine practice. Analyses of the association of platelet count with thrombotic risk in ET have mainly been based on results of retrospective studies of cytoreductive therapy. In an analysis of ET patients treated with busulfan, incidence of thrombotic events was significantly lower in patients who maintained a platelet count below 600,000/μL for more than 70% of the total time period [2]. In an analysis of 35 patients on long-term anagrelide therapy, all 7 thrombotic events occurred when platelet count was 400,000/μL or higher [3]. A retrospective analysis of ET patients treated with anagrelide showed that the hazard ratio for thrombotic complications increases when platelet count exceeds 574,000/μL [4]. In contrast, an Italian analysis of 657 patients with ET did not identify platelet count as a risk factor for thrombosis [5]. Similarly, an analysis of patients enrolled in the PT-1 trial, which compared the thromboprophylactic efficacy of hydroxyurea and anagrelide, showed no correlation between platelet count and thrombotic risk [6]. Yet another study in ET patients treated with anagrelide showed no difference in the incidence rate of thrombosis and hemorrhage between those who fulfilled the ELN criteria for CR and those who did not [7]. In conclusion, although the target platelet count is often set at 400,000 to 600,000/μL in routine practice, there is little evidence to support a target less than 400,000/μL.

References

1. Barosi G, et al. Revised response criteria for polycythemia vera and essential thrombocythemia: an ELN and IWG-MRT consensus project. Blood. 2013; 121(23): 4778–81. **(Review)**

2. Cortelazzo S, et al. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol. 1990; 8(3): 556–62. **(3iiiDi)**

3. Storen EC, et al. Long-term use of anagrelide in young patients with essential thrombocythemia. Blood. 2001; 97(4): 863–6. **(3iiiDi)**

4. Buxhofer-Ausch V, et al. Influence of platelet and white blood cell counts on major thrombosis—analysis from a patient registry in essential thrombocythemia. Eur J Haematol. 2016; 97(6): 511–6. **(3iiiDi)**

5. Carobbio A, et al. Leukocytosis and risk stratification assessment in essential thrombocythemia. J Clin Oncol. 2008; 26(16): 2732–6. **(3iiiDi)**

6. Campbell PJ, et al. Correlation of blood counts with vascular complications in essential thrombocythemia: analysis of the prospective PT1 cohort. Blood. 2012; 120(7): 1409–11. **(3iiiDi)**

7. Hernández-Boluda JC, et al. Clinical evaluation of the European LeukemiaNet response criteria in patients with essential thrombocythemia treated with anagrelide. Ann Hematol. 2013; 92(6): 771–5. **(3iiiDi)**

CQ 13 What is recommended as cytoreductive therapy for high-risk PV?

Recommendation grade: Category 2A Hydroxyurea is the drug of choice for cytoreductive therapy.
Recommendation grade: Category 1 Ruxolitinib is recommended in patients intolerant or resistant to hydroxyurea.

Explanation

In a study that compared PV outcomes in 51 patients newly treated with phlebotomy plus hydroxyurea to 134 historical controls previously treated with phlebotomy alone, the incidence rate of thrombosis for 795 weeks after the start of treatment was 9.8% with hydroxyurea plus phlebotomy versus 32.8% with phlebotomy alone, indicating that addition of hydroxyurea to treatment for PV reduces the incidence of thrombosis [1]. In a later retrospective study of propensity-matched PV patients who received phlebotomy alone versus hydroxyurea alone, the incidence of vascular events per 100 person-years was 5.8 with phlebotomy versus 3 with hydroxyurea, the incidence of disease transformation was 1.11 versus 0.05, and mortality was 0.32 versus 0.11, with all figures lower for hydroxyurea.[2] Although death and vascular events were less common in the low-risk group, hydroxyurea significantly reduced the incidence of these events in the high-risk group, indicating the benefit of hydroxyurea for high-risk PV. Patients treated with hydroxyurea are also more likely to achieve a hematocrit level below 45%, so hydroxyurea is recommended for high-risk patients.

Switching to ruxolitinib is recommended for patients intolerant or resistant to hydroxyurea. In a prospective RCT comparing ruxolitinib with best available treatment (BAT) in PV patients with splenomegaly who were intolerant or resistant to hydroxyurea, a hematocrit level below 45% was achieved in 60% of patients who received ruxolitinib versus 19.6% of those who received BAT, and a 35% or greater reduction in spleen volume in 38.2% versus 0.9% [3]. In another study, ruxolitinib remained effective after 5 years in 75% of patients in whom it was originally effective [4]. In another analysis, the number of thrombotic events per 100 person-years at 80 weeks after the start of treatment was 1.8 in patients treated with ruxolitinib versus 4.1 in patients crossed over from BAT to ruxolitinib (8.2 assuming no crossover), showing that promptly switching to ruxolitinib reduces the risk of thrombosis in patients intolerant or resistant to hydroxyurea [5]. Even among PV patients intolerant or resistant to hydroxyurea who did not have splenomegaly, the percentage achieving hematocrit control was superior with ruxolitinib compared with BAT (62% vs. 19%) [6].

A retrospective study of 15 patients with PV and 21 with ET demonstrated the benefit of busulfan for achieving hematologic remission in patients intolerant or resistant to hydroxyurea, but transformation to AML/MDS occurred in 3 patients (including 1 with PV) [7]. A prospective observational study conducted after the prospective study on the thromboprophylactic effect of hydroxyurea for high-risk ET showed that patients treated with hydroxyurea after busulfan have a higher risk of secondary cancer, and a Swedish registry study showed that the risk of transformation to AML/MDS from MPN increased 2.9-fold in patients who received 2 or 3 cytoreductive therapies, which indicates that careful management is required when using busulfan after hydroxyurea [8, 9].

The long-acting interferons, peg-IFN-α 2a [10] and ropeg-IFN-α 2b, [11, 12] have also achieved hematologic responses in previously untreated PV patients as well as those resistant or intolerant to hydroxyurea, though these drugs are not covered by Japanese NHI.

References

1. Fruchtman SM, et al. From efficacy to safety: a Polycythemia Vera Study group report on hydroxyurea in patients with polycythemia vera. Semin Hematol. 1997; 34(1): 17–23. **(3iiiC)**

2. Barbui T, et al. A reappraisal of the benefit-risk profile of hydroxyurea in polycythemia vera: A propensity-matched study. Am J Hematol. 2017; 92(11): 1131–6. **(3iiiC)**

3. Vannucchi AM, et al. Ruxolitinib versus standard therapy for the treatment of polycythemia vera. N Engl J Med. 2015; 372(5): 426–35. **(1iiDiv)**

4. Kiladjian JJ. Long-term efficacy and safety of ruxolitinib in polycythaemia vera—Authors' reply. Lancet Haematol. 2020; 7(7): e506. **(1iiDiv)**

5. Verstovsek S, et al. Ruxolitinib versus best available therapy in patients with polycythemia vera: 80-week follow up from the RESPONSE trial. Haematologica. 2016; 101(7): 821–9. **(1iiDiv)**

6. Passamonti F, et al. Ruxolitinib for the treatment of inadequately controlled polycythaemia vera without splenomegaly (RESPONSE-2): a randomised, open-label, phase 3b study. Lancet Oncol. 2017; 18(1): 88–99. **(1iiDiv)**

7. Alvarez-Larrán A, et al. Busulfan in patients with polycythemia vera or essential thrombocythemia refractory

or intolerant to hydroxyurea. Ann Hematol. 2014; 93(12): 2037–43. **(3iiiDiv)**

8. Finazzi G, et al. Second malignancies in patients with essential thrombocythaemia treated with busulphan and hydroxyurea: long-term follow-up of a randomized clinical trial. Br J Haematol. 2000; 110(3): 577–83. **(3iiiC)**

9. Björkholm M, et al. Treatment-related risk factors for transformation to acute myeloid leukemia and myelodysplastic syndromes in myeloproliferative neoplasms. J Clin Oncol. 2011; 29(17): 2410–5. **(3iC)**

10. Yacoub A, et al. Pegylated interferon alfa-2a for polycythemia vera or essential thrombocythemia resistant or intolerant to hydroxyurea. Blood. 2019; 134(18): 1498–509. **(3iiiDiv)**

11. Gisslinger H, et al. Ropeginterferon alfa-2b versus standard therapy for polycythaemia vera (PROUD-PV and CONTINUATION-PV): a randomised, non-inferiority, phase 3 trial and its extension study. Lancet Haematol. 2020; 7(3): e196-208. **(1iiDiv)**

12. Edahiro Y et al. Efficacy and safety of ropeginterferon alfa-2b in Japanese patients with polycythemia vera: an open-label, single-arm, phase 2 study. Int J Hematol. 2022; 116(2): 215–27 **(3iiDiv)**

CQ 14 What is recommended as cytoreductive therapy for high-risk ET?

Recommendation grade: Category 1
Hydroxyurea and anagrelide are recommended to prevent arterial and venous thrombosis and serious hemorrhage.

Explanation

High-risk ET patients are treated with cytoreductive therapy and antiplatelet therapy to prevent thrombosis. Hydroxyurea and anagrelide are options for cytoreductive drugs. Among these, hydroxyurea is the most commonly used in cytoreductive therapy. In an RCT, hydroxyurea significantly reduced the incidence of thrombosis over a 27-month follow-up period compared with observation (3.6% vs. 24%) [1]. Hydroxyurea and anagrelide have been directly compared in cytoreductive therapy for high-risk ET in two RCTs. One of these trials was conducted in 809 patients with ET diagnosed by the PVSG criteria, 82% of whom were previously treated. The conclusion of the trial was that anagrelide plus low-dose aspirin poses a lower risk of venous thrombosis than hydroxyurea plus low-dose aspirin, but yields shorter EFS due to high incidence of atrial thrombosis, serious hemorrhage, and progression to myelofibrosis [2]. The other trial was conducted in 253 previously untreated patients with ET diagnosed by the 2008 WHO classification who were undergoing primary therapy (most trial patients received anagrelide or hydroxyurea alone, but 28–29% received combination therapy with aspirin). Anagrelide and hydroxyurea had a similar incidence of thrombosis and hemorrhage, and their EFS did not differ significantly [3]. In a prospective observational study of 3611 high-risk ET patients, the number of thrombotic events per 100 person-years was lower with anagrelide than with other cytoreductive therapy (1.62 vs. 2.06), though these results require careful interpretation because the median age was just 56 years in the anagrelide group ($n = 804$) versus 70 years in the other cytoreductive therapy group ($n = 2807$, including 2341 treated with hydroxyurea) [4]. However, major hemorrhagic events were more common with anagrelide than with other cytoreductive therapy drugs (0.89 vs. 0.43). More than 80% of patients in the other cytoreductive therapy group received hydroxyurea. Considered alongside those of the prospective RCTs discussed above, both anagrelide and hydroxyurea are recommended as first-line cytoreductive therapy drugs for high-risk ET.

IFN-α is not covered by Japanese NHI, but has shown benefit for high-risk ET. In a single-arm study in 123 patients with high-risk ET, 90 patients had an overall hematologic response [5]. Peg-IFN-α 2b, a long-acting IFN, also has shown efficacy: in a single-arm trial of 36 patients with high-risk ET, 67% achieved platelet count control at 12 months [6].

References

1. Cortelazzo S, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. N Engl J Med. 1995; 332(17): 1132–6. **(1iiDi)**

2. Harrison CN, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005; 353(1): 33–45. **(1iiDi)**

3. Gisslinger H, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized controlled trial. Blood. 2013; 121(10): 1720–8. **(1iiDi)**

4. Birgegård G, et al. Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the Evaluation of Anagrelide Efficacy and Long-term Safety study. Haematologica. 2018; 103(1): 51–60. **(3iiiC)**

5. Huang BT, et al. Interferonα-2b gains high sustained response therapy for advanced essential thrombocythemia

and polycythemia vera with JAK2V617F positive mutation. Leuk Res. 2014; 38(10): 1177–83. **(ET: 3iiiDiv, PV: 1iiDiv)**

6. Langer C, et al.: Pegylated interferon for the treatment of high risk essential thrombocythemia: results of a phase II study. Haematologica. 2005; 90(10): 1333–8. **(3iiiDiv)**

CQ 15 What treatments are recommended for pregnant patients with ET/PV?

Recommendation grade: Category 2B
Intervention with low-dose aspirin is recommended. For high-risk pregnancies, addition of low molecular weight heparin (LMWH) (not covered by Japanese NHI) should be considered.

Explanation

In a meta-analysis of 22 studies that included 1210 pregnancies in 762 women with MPN, the live birth rate was 71.3%. This study included 159 pregnancies in women with PV and 815 in women with ET, and the live birth rates in these groups were 66.7% and 71.1%, respectively [1]. First-trimester miscarriages accounted for 59.1% of miscarriages. Another meta-analysis of pregnancy in women with ET (21 studies, 504 pregnant women, 756 pregnancies) showed very similar results, with a 74% live birth rate and 73% of miscarriages occurring in the first trimester [2]. These results show that early miscarriage is common in pregnant patients with PV/ET.

In the abovementioned systematic review on MPN during pregnancy, treatment with aspirin (227 patients) or IFN-α (90 patients) improved the live birth rate (OR 8.6 and 9.7, respectively) [2]. Addition of heparin to aspirin did not improve the live birth rate. One meta-analysis in patients with ET investigated maternal thrombosis and hemorrhage [2]. These events did not occur in any of 82 pregnancies when LMWH was used, compared to 8 of 407 pregnancies (2.5%) when LMWH was not used. Six events of antepartum venous thromboembolism occurred in 212 pregnancies (4.2%) when aspirin was used alone without heparin, compared to 0 events in 71 pregnancies when both heparin and aspirin were used. In the postpartum period, venous thromboembolism occurred in 0 of 96 pregnancies when LMWH was used, versus 6 of 229 pregnancies (4.4%) when LMWH was not used. Hemorrhagic events were observed in the antepartum period in 0% of 82 pregnancies when LMWH was used and 4.0% of 407 pregnancies when LMWH was not used. In the postpartum period, hemorrhagic events were observed in 2.9% of pregnancies regardless of whether LMWH was used.

Although no RCTs have compared intervention with no intervention, low-dose aspirin is recommended during pregnancy and for 6 weeks postpartum to prevent vascular thrombotic events and miscarriage in pregnant patients with ET/PV. Aspirin should be temporarily discontinued or switched to LMWH (not covered by Japanese NHI) 1 to 2 weeks before delivery. LMWH should be discontinued 12 to 24 h before delivery. It is important to work in close collaboration with the patient's obstetrician, including in deciding when to discontinue aspirin to prepare for anesthesia at delivery. At the same time, hematocrit should be maintained at < 45% for PV.

Pregnancies where the patient has a history of thrombosis, hemorrhage, previous miscarriage attributed to MPN, fetal developmental delay, stillbirth, placental insufficiency, serious eclampsia, or a platelet count persistently exceeding 1,500,000/μL are considered high-risk pregnancies. Addition of LMWH to aspirin is recommended for high-risk pregnancies with a history of major thrombosis or serious complications in a previous pregnancy, but aspirin should be discontinued if hemorrhage is observed. In patients with a platelet count exceeding 1,500,000/μL, IFN-α (not covered by Japanese NHI) should be used to reduce platelet count. The *JAK2* V617F mutation in particular is an independent predictor of miscarriage, and it is suggested that reducing platelet count using IFN-α may prevent complications [3]. Use of IFN-α should be considered for increased platelet count instead of aspirin in patients with a history of major hemorrhagic events. IFN-α is the preferred cytoreductive therapy drug. Hydroxyurea is contraindicated during pregnancy, and breastfeeding mothers should be instructed to stop breastfeeding before taking it.

In a Japanese case series of 10 pregnancies in 9 patients with ET who were treated with aspirin and IFN-α, all pregnancies resulted in healthy children [4].

References

1. Maze D, et al. Association of Treatments for Myeloproliferative Neoplasms During Pregnancy With Birth Rates and Maternal Outcomes: A Systematic Review and Meta-analysis. JAMA Netw Open. 2019; 2(10): e1912666. **(Review)**

2. Skeith L, et al. Risk of venous thromboembolism in pregnant women with essential thrombocythemia: a systematic review and meta-analysis. Blood. 2017; 129(8): 934–9. **(Review)**

3. Melillo L, et al. Outcome of 122 pregnancies in essential thrombocythemia patients: A report from the Italian registry. Am J Hematol. 2009; 84(10): 636–40. **(3iC)**

4. Edahiro Y, et al. Interferon therapy for pregnant patients with essential thrombocythemia in Japan. Int J Hematol. 2021; 113(1): 106–11. **(3iiiC)**

CQ 16 What risk classification systems are recommended for MF (PMF and post-PV/post-ET-MF)?

Recommendation grade: Category 2A The recommended risk classification systems for PMF are the IPSS, DIPSS, and DIPSS plus.
Recommendation grade: Category 2B The recommended risk classification system for post PV/post ET-MF is MYSEC-PM.

Explanation

Prognostic models for PMF include three versions of IPSS, which are based on clinical data, [1–3] the Genetically Inspired Prognostic Scoring System for Primary Myelofibrosis (GIPSS), [5] which is based on chromosomal abnormalities and mutation data, the Mutation-enhanced International Prognostic Score System for Transplantation-age Patients with Primary Myelofibrosis (MIPSS70), [5] which integrates clinical data and mutation data by setting the age of indication for transplantation at 70 years or younger, and the MIPSS70 Ver 2.0, [6] which incorporates new Hb thresholds based on cytogenetic abnormalities, mutations, and sex. As routine testing for high-molecular-risk mutations in *ASXL1*, *SRSF2*, *EZH2*, *IDH1*, *IDH2*, and *U2AF1* in PMF is not feasible, models based on clinical data are the most practical. These are the original IPSS, which comprises the 5 prognostic factors of age (> 65 years), clinical symptoms (e.g., weight loss, night sweats, and fever), Hb level (< 10 g/dL), WBC count at diagnosis (> 25,000/μL), and peripheral blast percentage (≥ 1%); [7] the DIPSS, which assigns different weights to these 5 factors; [7] and the DIPSS Plus, which adds cytogenetic abnormalities, platelet count, and transfusion dependence to the DIPSS [3]. The total score is used to classify the patient into one of four risk groups: Low, Int-1, Int-2, or High. In a study that applied these models to data from Japanese patients with PMF, the IPSS and DIPSS performed poorly for differentiating between the Int-2 and high-risk groups, but the DIPSS plus was able to differentiate these groups [8]. The current treatment guidelines, which divide patients into Low/Int-1-risk and Int-2/High-risk categories for treatment planning purposes, allow any classification system to be used for treatment selection, but the DIPSS plus is the most appropriate for Japanese patients because it offers more precise prognostic modeling.

Similar treatment approaches are used for PMF and post-PV/ET-MF because these entities have similar mutations and symptoms. Three studies that investigated the applicability of systems developed for PMF (IPSS, DIPSS, and DIPSS plus) to post-PV/ET-MF showed conflicting results: two studies showed that these systems are not applicable, but one study showed that they are applicable [9–11]. The MYSEC-PM, which was developed for post-PV/ET-MF, stratifies patients into 4 groups according to a score based on six independent unfavorable prognostic factors (age, Hb < 11 g/dL, peripheral blasts ≥ 3%, platelets < 150,000/μL, constitutional symptoms, and absence of *CALR* mutation), and was shown to be superior to the IPSS as a prognostic model for post-PV/ET-MF [12]. In a separate cohort, MYSEC-PM performed better than the IPSS for prognostic stratification of PET/PPV-MF [13]. The difference in treatment may impact the applicability of prognostic models. MYSEC-PM is also a useful prognostic model for post-PV/ET-MF treated with ruxolitinib [14].

References

1. Cervantes F, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 2009; 113(13): 2895–901. **(3iiA)**

1. Passamonti F, et al. Dynamic International Prognostic Scoring System (DIPSS) predicts progression to acute myeloid leukemia in primary myelofibrosis. Blood. 2010; 116(15): 2857–8. **(3iiA)**

2. Gangat N, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol. 2011; 29(4): 392–7. **(3iiA)**

3. Tefferi A, et al. GIPSS: genetically inspired prognostic scoring system for primary myelofibrosis. Leukemia. 2018; 32(7): 1631–42. **(3iiA)**

4. Guglielmelli P, et al. MIPSS70: Mutation-Enhanced International Prognostic Score System for Transplantation-Age Patients With Primary Myelofibrosis. J Clin Oncol. 2018; 36(4): 310–8. **(3iiA)**

5. Tefferi A, et al. MIPSS70 + Version 2.0: Mutation and Karyotype-Enhanced International Prognostic Scoring System for Primary Myelofibrosis. J Clin Oncol. 2018; 36(17): 1769–70. **(3iiA)**

6. Passamonti F, et al. A dynamic prognostic model to predict survival in primary myelofibrosis: a study by the

IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood. 2010; 115(9): 1703–8. **(3iiA)**

7. Takenaka K, et al. Clinical features and outcomes of patients with primary myelofibrosis in Japan: report of a 17-year nationwide survey by the Idiopathic Disorders of Hematopoietic Organs Research Committee of Japan. Int J Hematol. 2017; 105(1): 59–69. **(3iA)**

8. Masarova L, et al. Patients with post-essential thrombocythemia and post-polycythemia vera differ from patients with primary myelofibrosis. Leuk Res. 2017; 59: 110–6. **(3iiA)**

9. Hernández-Boluda JC, et al. The International Prognostic Scoring System does not accurately discriminate different risk categories in patients with post-essential thrombocythemia and post-polycythemia vera myelofibrosis. Haematologica. 2014; 99(4): e55-7. **(3iiA)**

10. Tefferi A, et al. Application of current prognostic models for primary myelofibrosis in the setting of post-polycythemia vera or post-essential thrombocythemia myelofibrosis. Leukemia. 2017; 31(12): 2851–2. **(3iiA)**

11. Passamonti F, et al. A clinical-molecular prognostic model to predict survival in patients with post polycythemia vera and post essential thrombocythemia myelofibrosis. Leukemia. 2017; 31(12): 2726–31. **(3iiA)**

12. Hernández-Boluda JC, et al. Performance of the myelofibrosis secondary to PV and ET-prognostic model (MYSEC-PM) in a series of 262 patients from the Spanish registry of myelofibrosis. Leukemia. 2018; 32(2): 553–5. **(3iiA)**

13. Palandri F, et al. Differences in presenting features, outcome and prognostic models in patients with primary myelofibrosis and post-polycythemia vera and/or post-essential thrombocythemia myelofibrosis treated with ruxolitinib. New perspective of the MYSEC-PM in a large multicenter study. Semin Hematol. 2018; 55(4): 248–55. **(3iiA)**

CQ 17 Is ruxolitinib recommended for MF (PMF and post-PV/post-ET-MF)?

(1) Low-risk MF (2) High-risk MF (3) Before allo-HSCT in transplant-eligible patients.

Recommendation grade: Category 2A (low-risk MF), Category 1 (high-risk MF), Category 2B (before HSCT in transplant-eligible patients)
Ruxolitinib is recommended for high-risk MF patients and for low-risk MF patients with splenomegaly or general symptoms. In patients eligible for allo-HSCT, consider ruxolitinib administration, taking into the account of timing of HSCT.

Explanation

Two randomized phase III trials of ruxolitinib, a JAK1/JAK2 inhibitor for PMF and post-PV/post-ET-MF, demonstrated the superiority of ruxolitinib to placebo or available therapy for reducing spleen volume (the primary endpoint) in patients whose risk group was Int-2 or higher and had splenomegaly (≥ 5 cm) and a platelet count of at least 100,000/μL. Ruxolitinib significantly reduced general symptoms as well [1, 2]. Results of long-term observation suggest that ruxolitinib also helps to improve OS [3]. An observational study of 1010 patients in the ERNEST study also showed a survival benefit with ruxolitinib (median survival time 6.7 years with ruxolitinib vs. 5.1 years with hydroxyurea) [4]. The survival benefit was observed in patients whose risk group was Int-2 or higher. Later, a phase IIIb expanded-access trial showed ruxolitinib to be effective in patients with platelet counts between 50,000 and 100,000/μL [5]. Based on these results, ruxolitinib is recommended for Int-2 or higher-risk MF patients who have splenomegaly and general symptoms. It is important to note that improvement in general symptoms can be achieved by a low dose of ruxolitinib, but other effects such as spleen volume reduction requires higher dose of ruxolitinib.

No published studies have directly compared survival benefit between ruxolitinib and allo-HSCT, so allo-HSCT is recommended for patients who are younger, do not have comorbidities, and have a suitable donor. The role of ruxolitinib before HSCT in transplant-eligible patients was investigated in small single-arm uncontrolled prospective studies and retrospective analyses, and their results show that ruxolitinib could improve performance status before HSCT, but its effect on post-transplant prognosis is unclear [6–9]. These studies suggest that patients who respond to ruxolitinib may have a better post-transplant prognosis. Preventive measures such as gradual dose reduction before starting conditional regimens should be taken to avoid rebound after discontinuation of ruxolitinib. The 3-year continuation rate of ruxolitinib in clinical trials to date has been about 50%, so

the timing of HSCT should also be taken into account when starting ruxolitinib therapy in transplant-eligible patients.

For low-risk MF: clinical trials that included Int-1 patients have demonstrated the efficacy of ruxolitinib for reducing spleen size and general signs and symptoms [5, 10, 11]. Therefore, ruxolitinib is also recommended for low-risk patients if they have splenomegaly or general symptoms. However, as with high-risk MF patients, the timing of HSCT should also be taken into account when starting ruxolitinib therapy for transplant-eligible patients.

References

1. Verstovsek S, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. N Engl J Med. 2012; 366(9): 799–807. **(1iC)**

2. Harrison C, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. N Engl J Med. 2012; 366(9): 787–98. **(1iC)**

3. Vannucchi AM, et al. A pooled analysis of overall survival in COMFORT-I and COMFORT-II, 2 randomized phase III trials of ruxolitinib for the treatment of myelofibrosis. Haematologica. 2015; 100(9): 1139–45. **(1iA)**

4. Guglielmelli P, et al. Impact of ruxolitinib on survival of patients with myelofibrosis in the real world: update of the ERNEST Study. Blood Adv. 2022; 6(2): 373–5. **(3iiiA)**

5. Al-Ali HK et al. Primary analysis of JUMP, a phase 3b, expanded-access study evaluating the safety and efficacy of ruxolitinib in patients with myelofibrosis, including those with low platelet counts. Br J Haematol. 2020; 189(5): 888–903. **(3iiiC)**

6. Kröger N, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. Leukemia. 2021; 35(12): 3551–60. **(3iiiC)**

7. Robin M, et al. Ruxolitinib before allogeneic hematopoietic transplantation in patients with myelofibrosis on behalf SFGM-TC and FIM groups. Bone Marrow Transplant. 2021; 56(8): 1888–99. **(2Dii)**

8. Shanavas M, et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis with Prior Exposure to Janus Kinase 1/2 Inhibitors. Biol Blood Marrow Transplant. 2016; 22(3): 432–40. **(3iiiA)**

9. Salit RB, et al. Pre-hematopoietic cell transplant Ruxolitinib in patients with primary and secondary myelofibrosis. Bone Marrow Transplant. 2020; 55(1): 70–6. **(3iiiA)**

10. Mead AJ, et al. Response to ruxolitinib in patients with intermediate-1-, intermediate-2-, and high-risk myelofibrosis: results of the UK ROBUST Trial. Br J Haematol. 2015; 170(1): 29–39. **(3iiiC)**

11. Kirito K, et al. Evaluation of the dose and efficacy of ruxolitinib in Japanese patients with myelofibrosis. Int J Hematol. 2018; 107(1): 92–7. **(3iiiC)**

CQ 18 Is allo-HSCT recommended for patients with MF (PMF and post-PV/post-ET-MF), and what are the recommended transplant sources and conditioning regimens?

Recommendation grade: Category 2B
Allo-HSCT is recommended for younger patients in the Int-2 or higher-risk group who do not have any comorbidities and have a suitable donor.

Explanation

At present, allo-HSCT is the only curative treatment option for MF (PMF and post-PV/post-ET-MF). Transplanted hematopoietic stem cells can engraft even in the presence of marked fibrosis in the bone marrow, and bone marrow fibrosis resolves with engraftment in over half of patients. Although most studies of allo-HSCT for MF have been retrospective analyses, many show an OS rate of 40% to 50%, [1–5] and long-term survival is achievable in patients who survive the first 2 years after transplantation [6] In an analysis using data from the Japanese Transplant Registry Unified Management Program (TRUMP), OS outcomes after first transplantation for PMF, by donor source, were 63% for related bone marrow, 43% for related peripheral blood, and 41% for unrelated bone marrow (5-year OS rates), and 36% for cord blood (2-year OS rate) [7]. These results clearly demonstrate that allo-HSCT can be curative for PMF and post-PV/post-ET-MF, and thus allo-HSCT is recommended in transplant-eligible patients.

A study that retrospectively analyzed survival rates among patients who received and did not receive allo-HSCT showed that mortality risk from allo-HSCT is lower for PMF patients whose DIPSS risk group is int-2 or high and who are younger than 65 years [1, 2, 5]. Consequently, allo-HSCT is recommended for patients younger than 65 years whose DIPSS risk group is int-2 or high. However, various issues with allo-HSCT have been noted, including that typical myeloablative conditioning has a high treatment-related mortality rate of 30% to 40%, and that the older age of onset results in few patients with PMF being eligible for transplantation. According to a 2015 consensus report by an EBMT/ELN international working group, allo-HSCT is indicated for PMF patients younger than 70 years whose risk group

is int-2 or high, and patients younger than 65 years whose group is int-1 and have criteria that put them at high risk for leukemic transformation (e.g., transfusion dependence, peripheral blasts > 1%, adverse cytogenetics, triple-negative disease, and the *ASXL1* mutation) [8].

As for stem cell sources, many studies have shown that risk of treatment-related (non-relapse) mortality after HSCT is higher when cells are obtained from an unrelated donor in comparison with an HLA-matched sibling donor [9–11]. In one prospective study of allo-HSCT with nonmyeloablative conditioning (MPD-RC101) with fludarabine and melphalan, and anti-thymocyte immunoglobulin (ATG) in unrelated transplants, transplant outcome from other than HLA-matched related donors was poor, with a higher rate of graft failure and lower survival rates, but recent studies are showing that the gap in transplant outcomes by cell source is shrinking. A retrospective analysis from Japan identified frequent transfusions before transplantation and use of cord blood grafts as risk factors for non-relapse mortality after transplantation, and found that infection was a major cause of death after cord blood transplantation [7]. However, stem cell source was not identified as a risk factor for all-cause mortality. Therefore, an HLA-matched unrelated donor or cord blood may be options for patients without an HLA-matched donor, though these choices increase the risk of non-relapse mortality. An increasing number of case reports on HSCT with HLA-haploidentical donor cells have been published, and these have been shown to be a stem cell source that can be selected for MF as well, but it is important to be aware of the risks of graft failure and non-relapse mortality [12–14].

Myeloablative and nonmyeloablative conditioning are both options, as retrospective analyses have shown no difference in OS between the two, but myeloablative conditioning is recommended for younger patients because it offers better GVHD-free and relapse-free survival [10, 11, 15, 16]. The optimal conditioning regimen is unclear due to a lack of prospective studies on allo-HSCT for MF. The main regimens used for nonmyeloablative conditioning are fludarabine plus busulfan or fludarabine plus melphalan, but various aspects remain to be clarified, including the optimal doses of these drugs and the need (and doses) for ATG and total body irradiation.

Although the JAK1/JAK2 inhibitor ruxolitinib shows promise for reducing general symptoms and tumor burden before transplantation, there is no evidence regarding whether it improves post-transplant outcomes. No analyses conducted to date have identified ruxolitinib as a factor affecting post-transplant outcomes [17–20]. Good results can be expected when spleen size is reduced before transplantation, [21] and factors such as the ruxolitinib continuation rate should be considered when determining the need for ruxolitinib treatment before transplantation and the timing of transplantation after starting ruxolitinib.

Splenomegaly is one factor that contributes to graft failure in allo-HSCT for MF. However, no consensus has been reached regarding how pre-transplantation splenectomy or irradiation aimed at reducing spleen size impact post-transplant relapse and survival [22, 23]. It has recently become common practice to use ruxolitinib to reduce spleen size, which is reducing the role of pre-transplant splenectomy and splenic irradiation.

References

1. Scott BL, et al. The Dynamic International Prognostic Scoring System for myelofibrosis predicts outcomes after hematopoietic cell transplantation. Blood. 2012; 119(11): 2657–64. **(3iiiA)**

2. Kröger N, et al. Impact of allogeneic stem cell transplantation on survival of patients less than 65 years of age with primary myelofibrosis. Blood. 2015; 125(21): 3347–50; quiz 3364. **(3iiiA)**

3. Kröger N, et al. Impact of Molecular Genetics on Outcome in Myelofibrosis Patients after Allogeneic Stem Cell Transplantation. Biol Blood Marrow Transplant. 2017; 23(7): 1095–101. **(3iiiA)**

4. Ali H, et al. MIPSS70 + v2.0 predicts long-term survival in myelofibrosis after allogeneic HCT with the Flu/Mel conditioning regimen. Blood Adv. 2019; 3(1): 83–95. **(3iiiA)**

5. Gowin K, et al. Survival following allogeneic transplant in patients with myelofibrosis. Blood Adv. 2020; 4(9): 1965–73. **(3iiiA)**

6. Robin M, et al. Long-term outcome after allogeneic hematopoietic cell transplantation for myelofibrosis. Haematologica. 2019; 104(9): 1782–8. **(3iiiA)**

7. Murata M, et al. Comparison of Outcomes of Allogeneic Transplantation for Primary Myelofibrosis among Hematopoietic Stem Cell Source Groups. Biol Blood Marrow Transplant. 2019; 25(8): 1536–43. **(3iiiDii)**

8. Kröger NM, et al. Indication and management of allogeneic stem cell transplantation in primary myelofibrosis: a consensus process by an EBMT/ELN international working group. Leukemia. 2015; 29(11): 2126–33. **(Review)**

9. Hernández-Boluda JC, et al. Determinants of survival in myelofibrosis patients undergoing allogeneic hematopoietic cell transplantation. Leukemia. 2021; 35(1): 215–24. **(3iiiA)**

10. Gupta V, et al. Reduced-intensity hematopoietic cell transplantation for patients with primary myelofibrosis: a cohort analysis from the center for international blood and marrow transplant research. Biol Blood Marrow Transplant. 2014; 20(1): 89–97. **(3iiiA)**

11. Rondelli D, et al. MPD-RC 101 prospective study of reduced-intensity allogeneic hematopoietic stem cell transplantation in patients with myelofibrosis. Blood. 2014; 124(7): 1183–91. **(3iiiA)**

12. Hernández-Boluda JC, et al. Predicting Survival after Allogeneic Hematopoietic Cell Transplantation in Myelofibrosis: Performance of the Myelofibrosis Transplant Scoring System (MTSS) and Development of a New Prognostic Model. Biol Blood Marrow Transplant. 2020; 26(12): 2237–44. **(3iiiA)**

13. Kunte S, et al., Allogeneic blood or marrow transplantation with haploidentical donor and post-transplantation cyclophosphamide in patients with myelofibrosis: a multicenter study. Leukemia. 2022; 36(3): 856–64. **(3iiiA)**

14. Raj K, et al. Family Mismatched Allogeneic Stem Cell Transplantation for Myelofibrosis: Report from the Chronic Malignancies Working Party of European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019; 25(3): 522–8. **(3iiiA)**

15. Kröger N, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2009; 114(26): 5264–70. **(3iiiDii)**

16. McLornan D, et al. Myeloablative and Reduced-Intensity Conditioned Allogeneic Hematopoietic Stem Cell Transplantation in Myelofibrosis: A Retrospective Study by the Chronic Malignancies Working Party of the European Society for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2019; 25(11): 2167–71. **(3iiiA)**

17. Shanavas M, et al. Outcomes of Allogeneic Hematopoietic Cell Transplantation in Patients with Myelofibrosis with Prior Exposure to Janus Kinase 1/2 Inhibitors. Biol Blood Marrow Transplant. 2016; 22(3): 432–40. **(3iiiA)**

18. Shahnaz Syed Abd Kadir S, et al. Impact of ruxolitinib pretreatment on outcomes after allogeneic stem cell transplantation in patients with myelofibrosis. Eur J Haematol. 2018; 101(3): 305–17. **(3iiiA)**

19. Gupta V, et al. Ruxolitinib Therapy Followed by Reduced-Intensity Conditioning for Hematopoietic Cell Transplantation for Myelofibrosis: Myeloproliferative Disorders Research Consortium 114 Study. Biol Blood Marrow Transplant. 2019; 25(2): 256–64. **(3iiiDii)**

20. Robin M, et al. Ruxolitinib before allogeneic hematopoietic transplantation in patients with myelofibrosis on behalf SFGM-TC and FIM groups. Bone Marrow Transplant. 2021; 56(8): 1888–99. **(2Dii)**

21. Kröger N, et al. Impact of prior JAK-inhibitor therapy with ruxolitinib on outcome after allogeneic hematopoietic stem cell transplantation for myelofibrosis: a study of the CMWP of EBMT. Leukemia. 2021; 35(12): 3551–60. **(3iiiA)**

22. Polverelli N, et al. Impact of spleen size and splenectomy on outcomes of allogeneic hematopoietic cell transplantation for myelofibrosis: A retrospective analysis by the chronic malignancies working party on behalf of European society for blood and marrow transplantation (EBMT). Am J Hematol. 2021; 96(1): 69–79. **(3iiiA)**

23. Bossard JB, et al. Splenectomy before allogeneic hematopoietic cell transplantation for myelofibrosis: A French nationwide study. Am J Hematol. 2021; 96(1): 80–8. **(3iiiDiv)**

CQ 19 What treatments are recommended for leukemic transformation of MF (PMF and PV/post-ET-MF)?

Recommendation grade: Category 2B
Induction therapy should be performed with a standard AML regimen, and allo-HSCT should be considered for transplant-eligible patients.

Explanation

Treatment recommendations for leukemic transformation of MF are not clear at this time due to limited evidence. Relatively large retrospective studies have shown that chemotherapy has poor efficacy in patients with acute leukemia transformed from MF, with median survival at 2.6 to 3.6 months [1, 2].

In a retrospective analysis of 410 patients in the Mayo-AGIMM study, the 5-year OS rate was 10% in patients who underwent allo-HSCT ($n = 24$), versus 13% in patients who achieved remission with induction therapy but did not undergo allo-HSCT ($n = 24$) and 1% in patients who did not achieve remission and did not undergo allo-HSCT ($n = 200$). This indicates that the long-term prognosis is very poor without allo-HSCT, even when induction therapy is successful [2]. No clinical trial has investigated allo-HSCT for leukemic transformation of MF, but retrospective analyses have shown survival rates of approximately 20% to 30% at 3 to 5 years after transplantation (albeit with high rates of treatment-related mortality and relapse) which suggests that allo-HSCT can be curative [2–5]. Retrospective analyses have shown inconsistent results regarding whether remission status before transplantation affects long-term prognosis after transplantation.

The NCCN guidelines state that patients eligible for allo-HSCT should participate in a clinical trial or undergo HSCT after achieving remission through induction therapy, and add that an acute leukemia style intensive

chemotherapy regimen that includes a demethylating agent alone or in combination with ruxolitinib should be used for induction.[6] For transplant-ineligible patients, options include clinical trial participation, a demethylating agent alone or in combination with ruxolitinib, and low-dose chemotherapy.

The Mayo-AGIMM study reported a 35% remission rate with AML-style intensive chemotherapy in patients with leukemic transformation of MF, but as mentioned above, the 5-year OS rate was just 10% in patients who did not subsequently undergo allo-HSCT, and many patients relapse even after achieving remission [2]. In retrospective analyses of patients treated with the demethylating agent azacitidine, the overall response rate was a somewhat good 32% to 62%, but response duration was short, which highlights the need to develop consolidation therapy after azacitidine treatment [7–9]. Combination therapy with the demethylating agent decitabine and the JAK1/JAK2 inhibitor ruxolitinib yields an overall response rate of 44% to 61%, which is similar to that of intensive induction therapy, which indicates that it could become a bridge therapy to allo-HSCT for transplant-eligible patients [10–12]. Venetoclax, a BCL-2 inhibitor recently approved for AML, may also be useful as a bridge therapy to allo-HSCT in some patients when combined with a demethylating agent, although this has only been investigated in small retrospective analyses [13–15].

On the basis of the above evidence, it is recommended to treat leukemic transformation of MF with a standard AML regimen of azacitidine plus venetoclax or intensive chemotherapy for induction, and to consider allo-HSCT for transplant-eligible patients.

References

1. Mesa RA, et al. Leukemic transformation in myelofibrosis with myeloid metaplasia: a single-institution experience with 91 cases. Blood. 2005; 105(3): 973–7. **(3iiiC)**

2. Tefferi A, et al. Blast phase myeloproliferative neoplasm: Mayo-AGIMM study of 410 patients from two separate cohorts. Leukemia. 2018; 32(5): 1200–10. **(3iiiA)**

3. Alchalby H, et al. Allogeneic stem cell transplantation for myelofibrosis with leukemic transformation: a study from the Myeloproliferative Neoplasm Subcommittee of the CMWP of the European Group for Blood and Marrow Transplantation. Biol Blood Marrow Transplant. 2014; 20(2): 279–81. **(3iiiA)**

4. Cahu X, et al. Allo-SCT for Philadelphia-negative myeloproliferative neoplasms in blast phase: a study from the Societe Francaise de Greffe de Moelle et de Therapie Cellulaire (SFGM-TC). Bone Marrow Transplant. 2014; 49(6): 756–60. **(3iiiA)**

5. Gupta V, et al. Genetic factors rather than blast reduction determine outcomes of allogeneic HCT in BCR-ABL-negative MPN in blast phase. Blood Adv. 2020; 4(21): 5562–73. **(3iiiA)**

6. NCCN Clinical Practice Guidelines in Oncology. Myeloproliferative neoplasms Version 1.2022. **(Guidelines)**

7. Thepot S, et al. Treatment of progression of Philadelphia-negative myeloproliferative neoplasms to myelodysplastic syndrome or acute myeloid leukemia by azacitidine: a report on 54 cases on the behalf of the Groupe Francophone des Myelodysplasies (GFM). Blood. 2010; 116(19): 3735–42. **(3iiiDiv)**

8. Andriani A, et al. Azacytidine for the treatment of retrospective analysis from the Gruppo Laziale for the study of Ph-negative MPN. Leuk Res. 2015; 39(8): 801–4. **(3iiiDiv)**

9. Andriani A, et al. Treatment of Philadelphia-negative myeloproliferative neoplasms in accelerated/blastic phase with azacytidine. Clinical results and identification of prognostic factors. Hematol Oncol. 2019; 37(3): 291–5. **(3iiiA)**

10. Rampal RK, et al. Safety and efficacy of combined ruxolitinib and decitabine in accelerated and blast-phase myeloproliferative neoplasms. Blood Adv. 2018; 2(24): 3572–80. **(3iiiDiv)**

11. Bose P, et al. A phase 1/2 study of ruxolitinib and decitabine in patients with post-myeloproliferative neoplasm acute myeloid leukemia. Leukemia. 2020; 34(9): 2489–92. **(3iiiDiv)**

12. Mascarenhas JO, et al. Phase 2 study of ruxolitinib and decitabine in patients with myeloproliferative neoplasm in accelerated and blast phase. Blood Adv. 2020; 4(20): 5246–56. **(3iiiDiv)**

13. Masarova L, et al. Single-center experience with venetoclax combinations in patients with newly diagnosed and relapsed AML evolving from MPNs. Blood Adv. 2021; 5(8): 2156–64. **(3iiiDiv)**

14. Tremblay D, et al. Venetoclax and hypomethylating agent combination therapy in acute myeloid leukemia secondary to a myeloproliferative neoplasm. Leuk Res. 2020; 98: 106,456. **(3iiiC)**

15. Gangat N, et al. Venetoclax with azacitidine or decitabine in blast-phase myeloproliferative neoplasm: A multicenter series of 32 consecutive cases. Am J Hematol. 2021; 96(7): 781–9. **(3iiiDiv)**

CQ 20 What treatments are recommended for pre-PMF?

Recommendation grade: Category 3 Although clear evidence does not exist at this time, it is recommended to plan treatment based on the prognostic classification for PMF.
Recommendation grade: Category 3 Thromboprophylaxis should be considered for patients with a history of thrombosis or cardiovascular risk.

Explanation

The 2017 WHO classification lists separate diagnostic criteria for two categories of PMF: prefibrotic PMF (pre-PMF) and overt PMF. These criteria emphasize pathological findings on bone marrow biopsy, especially fibrosis, and define pre-PMF as having no more than a grade 1 increase in reticular fibers. Careful differentiation from ET is necessary to ensure an accurate prognosis.

At this time, the ELN and NCCN guidelines do not propose specific treatments for pre-PMF. Therefore, it is currently recommended to base the treatment plan for pre-PMF on a prognostic classification such as the IPSS, as is done for PMF [1]. However, a retrospective analysis showed that although the IPSS is also a useful prognostic classification for pre-PMF, it is not sufficient to differentiate between low-risk and high-risk groups, which is important to consider in treatment planning [2]. In addition, several retrospective studies have shown that incidence of thrombotic and hemorrhagic events may be higher in pre-PMF, [3–5] and one study showed that the International Prognostic Score of Thrombosis for ET (IPSET-thrombosis) and revised IPSET-thrombosis systems used for thrombosis risk classification in ET are also useful for thrombosis risk assessment in pre-PMF [6] which supports the validity of thromboprophylaxis in patients with high thrombotic risk.

References

1. Finazzi G, et al. Prefibrotic myelofibrosis: treatment algorithm 2018. Blood Cancer J. 2018; 8(11): 104. **(Review)**

2. Guglielmelli P, et al. Presentation and outcome of patients with 2016 WHO diagnosis of prefibrotic and overt primary myelofibrosis. Blood. 2017; 129(24): 3227–36. **(3iiA)**

3. Buxhofer-Ausch V, et al. Leukocytosis as an important risk factor for arterial thrombosis in WHO-defined early/prefibrotic myelofibrosis: an international study of 264 patients. Am J Hematol. 2012; 87(7): 669–72. **(3iiDi)**

4. Finazzi G, et al. Incidence and risk factors for bleeding in 1104 patients with essential thrombocythemia or prefibrotic myelofibrosis diagnosed according to the 2008 WHO criteria. Leukemia. 2012; 26(4): 716–9. **(3iiDi)**

5. Barbui T, et al. Disease characteristics and clinical outcome in young adults with essential thrombocythemia versus early/prefibrotic primary myelofibrosis. Blood. 2012; 120(3): 569–71. **(3iiDi)**

6. Guglielmelli P, et al. Validation of the IPSET score for thrombosis in patients with prefibrotic myelofibrosis. Blood Cancer J. 2020; 10(2): 21. **(3iiDi)**

Declarations

Conflict of interest KS has received per diem, including speaking fees, from Novartis Pharma, Takeda Pharmaceuticals, and Meiji Seika Pharma; has received research funding from EPS International, AbbVie, PharmaEssentia Japan, AstraZeneca, and Kowa; and has received scholarship or grant donations from Chugai Pharmaceutical, AbbVie, the Shinnihon Foundation of Advanced Medical Treatment Research, the Japanese Society of Hematology, Life Science Foundation of Japan, and Setsuro Fujii Memorial Osaka Foundation for Promotion of Fundamental Medical Research. NT has received per diem, including speaking fees, from Pfizer, Novartis Pharma, and Otsuka Pharmaceutical; has received research funding from Pfizer, Novartis Pharma, Otsuka Pharmaceutical, and Astellas Pharma; and has received scholarship or grant donations from Astellas Pharma, Mochida Pharmaceutical, Asahi Kasei Pharma, and Otsuka Pharmaceutical. NI has received per diem, including speaking fees, from Bristol Myers Squibb and Novartis Pharma. TK has received per diem, including speaking fees, from Alexion Pharmaceuticals. SK has received per diem, including speaking fees, from Bristol Myers Squibb, Pfizer, Novartis Pharma, and Otsuka Pharmaceutical; has received research funding from Ohara Pharmaceutical, Bristol Myers Squibb, and Pfizer; and has received scholarship or grant donations from Chugai Pharmaceutical, Kyowa Kirin, Taiho Pharmaceutical, Nippon Kayaku, Takeda Pharmaceuticals, Asahi Kasei Phama, Daiichi Sankyo, Mochida Pharmaceutical, and Otsuka Pharmaceutical. KK has received per diem, including speaking fees, from Takeda Pharmaceuticals. KT has received per diem, including speaking fees, from Novartis Pharma, MSD, Kyowa Kirin, Takeda Pharmaceuticals, Janssen Pharmaceutical, Otsuka Pharmaceutical, Astellas Pharma, Ono Pharmaceutical, Chugai Pharmaceutical, and Bristol Myers Squibb and has received research funding from Kyowa Kirin, Chugai Pharmaceutical, Otsuka Pharmaceutical, Asahi Kasei Phama, Daiichi Sankyo, and Japan Blood Products Organization.