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GUIDELINE

JSH Practical Guidelines for Hematological Malignancies, 2018: I. 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)

Staging of CML

Chronic myeloid leukemia (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.[1] 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 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 2017 World Health Organization

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(WHO) Classification[2] or the 2013 European LeukemiaNet (ELN) classification[3] (Table 1).

Prognostic classification for CML

Scoring systems include the four-factor Sokal score, which is calculated from age at presentation, spleen size (cm below costal margin), platelet count, and peripheral blasts (%),[4] and the six-factor Hasford score,[5] which is calculated from age, spleen size (cm below costal margin), peripheral blasts (%), peripheral eosinophils (%), peripheral basophils (%), and platelet count. These were used in the era of chemotherapy and interferon alpha (IFNα), but are also useful for imatinib therapy. They are used to classify patients into three risks groups: low, intermediate, and high (https://www.leukemia-net.org/content/leukemias/cml/euro__and_sokal_score/index_eng.html). The EUTOS score,[6] a two-group prognostic scoring system developed through analysis of patients treated with imatinib, is calculated from just two factors: basophils (%) and spleen size at presentation (7 × basophils [%] + 4 × spleen size [cm]). Patients with a score of 87 or lower are classified as low risk, and patients with a score higher than 87 are classified as high risk (http://www.leukemia-net.org/content/leukemias/cml/eutos_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 2013 ELN criteria (Table 2).[3]

Response to treatment for CML-CP is assessed at three levels: hematologic response (HR), cytogenetic response (CyR), and molecular response (MR) (Table 2). HR is determined from improvement in peripheral blood findings, CyR from the percentage of Ph-positive cells in the bone marrow, and MR from the amount of *BCR–ABL1* mRNA in blood cells determined by the polymerase chain reaction (PCR).

Table 1 Staging of CML by the 2017 WHO classification and 2013 ELN recommendations

Accelerated phase	
WHO Classification[2]	Meets ≥ 1 of the following hematological/cytogenetic criteria or provisional criteria concerning response to TKI criteria Haematological/cytogenetic criteria: Persistent or increasing high white blood cell counts (> 10×10^9/L), unresponsive to therapy Persistent or increasing splenomegaly, unresponsive to therapy Persistent thrombocytosis (> 1000×10^9/L), unresponsive to therapy Persistent thrombocytopenia (< 100,000/μL) unrelated to therapy ≥ 20% basophils in the peripheral blood 10–19% blasts in the peripheral blood and/or bone marrow Additional clonal chromosomal abnormalities in Philadelphia (Ph) chromosome-positive cells at diagnosis, including so-called major route abnormalities (a second Ph chromosome, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype, and abnormalities of 3q26.2 Any new clonal chromosomal abnormality in Ph + cells that occurs during therapy Provisional response-to-TKI criteria: Hematological resistance (or failure to achieve a complete hematological response) to the first TKI Any hematological, cytogenetic, or molecular indications of resistance to two sequential TKIs Occurrence of two or more mutations in the *BCR–ABL1* fusion gene during TKI therapy
ELN Classification[3]	Meets any one of the following criteria: 15–29% blasts in peripheral blood or bone marrow, or 30% or more blasts and promyelocytes ≥ 20% basophils in peripheral blood Persistent thrombocytopenia (< 100,000/μL) unrelated to therapy Additional chromosomal abnormalities (major route) in Ph + cells during therapy
Blast phase	
WHO Classification	Meets any one of the following criteria: ≥ 20% blasts in the peripheral blood or bone marrow An infiltrative proliferation of blasts in an extramedullary site (Imminent blast crisis should be suspected and further genetic testing is required if an obvious increase in lymphoblasts is detected in peripheral blood or bone marrow)
ELN Classification	Meets any one of the following criteria: ≥ 30% blasts in the peripheral blood or bone marrow Extramedullary disease

Table 2 Response assessment criteria for CML

Hematologic response (HR)		Blood and bone marrow test findings and clinical findings
Chronic-phase CML	Complete HR: CHR	WBC < 10,000/μL PLT < 450,000/μL No blasts or promyelocytes in peripheral blood Peripheral myelocytes + metamyelocytes = 0% Basophils < 5% No splenomegaly or hepatomegaly, no extramedullary disease
Advanced phase CML (Accelerated-phase + blast-phase)	Complete HR: CHR	WBC ≤ upper limit of reference range Neutrophils ≥ 1000/μL PLT ≥ 100,000/μL No blasts or promyelocytes in peripheral blood ≤ 5% blasts in bone marrow Myelocytes + metamyelocytes < 5% in peripheral blood Basophils < 20% No splenomegaly or hepatomegaly, no extramedullary disease
	No evidence of leukemia (NEL)	WBC ≤ upper limit of reference range No blasts or promyelocytes in peripheral blood ≤ 5% blasts in bone marrow Peripheral myelocytes + metamyelocytes < 5% Basophils < 20%No splenomegaly or hepatomegaly, no extramedullary disease

Cytogenetic response (CyR)	Percentage of Ph chromosome (*BCR–ABL1*) positive nucleated bone marrow cells (%)
Major cytogenetic response: MCyR	0–35
Complete cytogenetic response: CCyR	0
Partial cytogenetic response: PCyR	1–35
Minor cytogenetic response: minor CyR	36–65
Minimal cytogenetic response: minimal CyR	66–95
"None" cytogenetic response: no CyR	> 95

Molecular response (MR)	*BCR–ABL1*^{IS*2} gene level (by RT-PCR) (%)
Major molecular response: MMR	*BCR–ABL1*^{IS*2} ≤ 0.1
Deep molecular response: DMR[*1]	
MR$^{4.0}$	*BCR–ABL1*^{IS} ≤ 0.01
MR$^{4.5}$	*BCR–ABL1*^{IS} ≤ 0.0032
MR$^{5.0}$	*BCR–ABL1*^{IS} ≤ 0.001

[*1]The response level defined as complete molecular response (CMR) in the old 2009 ELN recommendations

[*2]*BCR–ABL1*^{IS}: Value standardized to the International Scale

Although different criteria for HR are used for CML-AP/BP and CML-CP, the same criteria are used for CyR and MR.

Overview of treatments for CML

1. BCR–ABL1 tyrosine kinase inhibitors (TKIs): TKIs that work by selectively inhibiting BCR–ABL1 tyrosine kinase and show superior hematologic, cytogenetic, and molecular efficacy include imatinib,[7–10] nilotinib,[11] and dasatinib.[12] Results of a trial that compared imatinib with interferon alpha plus low-dose cytarabine over a 5-year follow-up period led to the establishment of imatinib as the first-line drug for newly diagnosed CML-CP in place of interferon alpha.[8] Imatinib has also yielded superior long-term outcomes in Japan.[10]
2. Nilotinib and dasatinib are second-generation TKIs developed to treat CML resistant or intolerant to imatinib. However, trials comparing these drugs to imatinib have shown that they can also be selected to treat newly diagnosed CML-CP.[11,12]
3. Patients resistant or intolerant to the first-line TKI (imatinib, nilotinib, or dasatinib) are candidates for a different TKI. When a patient is TKI resistant, *BCR–*

ABL1 point mutation analysis is recommended to select a TKI to which that clone is sensitive. When a patient is TKI-intolerant, drug selection is based on adverse events caused by TKIs. Options for second-line and subsequent treatment are not only imatinib, nilotinib, and dasatinib but also the second-generation TKI bosutinib and the third-generation TKI ponatinib. As imatinib is a less potent inhibitor of ABL kinase than second-generation TKIs, switching to imatinib is not recommended when switching due to resistance. Bosutinib is effective in second- and third-line therapy for patients with *ABL1* mutations other than T315I, and is also well tolerated.[13,14] Ponatinib is effective in third-line therapy for patients with *ABL1* mutations including T315I, as well as patients resistant or intolerant to prior therapy.[15]

4. Allogeneic hematopoietic stem cell transplantation (allo-HSCT): although this treatment is potentially curative, its risk of early death from treatment-related toxicity must be considered. Therefore, it is only indicated for TKI-resistant CML-AP/BP that has progressed from CML-CP or for newly diagnosed CML-BP. Other eligibility criteria that must be considered are availability of a suitable donor and ability of the patient to tolerate transplantation-related toxicity as determined from age and performance status.[16]
5. Interferon alpha: Interferon alpha alone[17] or in combination with low-dose cytarabine[8] was the standard therapy for CML before the era of imatinib. Disappearance of the Ph chromosome is observed in some patients treated with interferon alpha, and it is known to improve overall survival. However, interferon alpha is not recommended for TKI-treatable CML in these Guidelines. In Japan, interferon alpha has and continues to be exclusively used to treat patients resistant or intolerant to all TKIs who are also ineligible for allo-HSCT, patients who achieved a molecular response on interferon alpha before the advent of TKI therapy, and pregnant patients who cannot use TKIs.

Monitoring of response to treatment for CML

Monitoring of response to treatment for CML with TKIs is conducted using the 2013 ELN recommendations.[3] The following methods are used for response assessment. CyR can be assessed by cytogenetic testing of bone marrow cells as well as fluorescence in situ hybridization (FISH) of peripheral neutrophils. MR is assessed by determining the level of *BCR–ABL1* expression by quantitative reverse transcriptase polymerase chain reaction (RT-PCR) with peripheral blood cells. The ratio of *BCR–ABL1* to *ABL* or another target gene is standardized to the International Scale 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 less than 1% 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 3). Monitoring should be performed frequently in case of warning, and changing treatments should be considered in case of treatment failure.

When switching from first-line treatment with imatinib to a second-generation TKI, an optimal response is defined as *BCR–ABL1*^{IS} of 10% or lower (Minor CyR) at 3 months, *BCR–ABL1*^{IS} of 10% or lower (or MCyR) at 6 months, *BCR–ABL1*^{IS} of 1% or lower (or CCyR) at 12 months, and *BCR–ABL1*^{IS} of 0.1% or lower after that point (Table 4).

Table 3 Response to first-line treatment for CML with a TKI (2013 European LeukemiaNet recommendations)

Timing of evaluation	Response		
	Optimal	Warning	Failure
Before treatment (baseline)	Not specified	High risk, or CCA/Ph+, major route	Not specified
3 months	*BCR–ABL1*^{IS} ≤ 10%, or Ph+ ≤ 35%	*BCR–ABL1*^{IS} > 10%, or Ph+ = 36–95%	CHR not achieved, or Ph+ > 95%
6 months	*BCR–ABL1*^{IS} < 1%, or Ph+ = 0%	*BCR–ABL1*^{IS} = 1–10%, or Ph+ = 1–35%	*BCR–ABL1*^{IS} > 10%, or Ph^{+} > 35%
12 months	*BCR–ABL1*^{IS} ≤ 0.1%	*BCR–ABL1*^{IS} > 0.1–1%	*BCR–ABL1*^{IS} > 1%, or Ph+ > 0%
Then and at any time	*BCR–ABL1*^{IS} ≤ 0.1%	CCA/Ph− (−7 or 7q−)	Loss of CHR, loss of CCyR, confirmed loss of MMR*, *ABL1* mutation, CCA/Ph+

MMR corresponds to *BCR–ABL1*^{IS} ≤ 0.1%, which is a response of MR$^{3.0}$ or better

*Confirmed loss of MMR requires two consecutive results showing *BCR–ABL1*^{IS} > 0.1%, of which one is ≥ 1%

CCA/Ph+: Clonal chromosomal abnormality in Ph+ cells CCA/Ph-: Clonal chromosomal abnormalities in Ph- cells

Table 4 Response to second-line treatment for CML with a TKI after failure of treatment with imatinib (2013 European LeukemiaNet recommendations)

Timing of evaluation	Response		
	Optimal	Warning	Failure
Before treatment (baseline)	Not specified	CHR not achieved or CHR lost after imatinib therapy, CyR not achieved with initial TKI therapy, or high risk	Not specified
3 months	*BCR–ABL1*$^{IS} \leq 10\%$, or Ph+ < 65%	*BCR–ABL1*$^{IS} > 10\%$, or Ph+ = 65–95%	CHR not achieved, or Ph+ > 95%, or new *ABL1* mutation
6 months	*BCR–ABL1*$^{IS} \leq 10\%$, or Ph+ < 35%	Ph+ = 35–65%	*BCR–ABL1*$^{IS} > 10\%$, or Ph+ > 65%, or new *ABL1* mutation
12 months	*BCR–ABL1*$^{IS} < 1\%$, or Ph+ = 0%	*BCR–ABL1*^{IS} = 1–10%, or Ph+ = 1–35%	*BCR–ABL1*$^{IS} > 10\%$, or Ph+ > 35%, or new *ABL1* mutation
Then, and at any time	*BCR–ABL1*$^{IS} \leq 0.1\%$	CCA/Ph− (−7 or 7q−), or *BCR–ABL1*$^{IS} > 0.1\%$	Loss of CHR, loss of CCyR, confirmed loss of MMR*, new *ABL1* mutation, CCA/Ph+

MMR corresponds to *BCR–ABL1* $^{IS} \leq 0.1\%$, which is a response of $MR^{3.0}$ or better

*Confirmed loss of MMR requires two consecutive results showing *BCR–ABL1* > 0.1%, of which one is ≥ 1%

CCA/Ph+: clonal chromosomal abnormality in Ph+ cells, CCA/Ph−: clonal chromosomal abnormalities in Ph- cells

In the ELN 2009 recommendations,[18] a complete molecular response (CMR) was defined as undetectable *BCR–ABL1*^{IS}. The ELN 2013 recommendations,[3] however, define *BCR–ABL1*^{IS} of 0.01% or lower as MR^4, 0.0032% or lower as $MR^{4.5}$, and 0.001% or lower as MR^5.[19] It is important to achieve at least MMR when treating CML-CP, and quantitative RT-PCR is also considered an essential test in guidelines for CML treatment outside Japan published by organizations such as the ELN and NCCN. The ELN criteria also list cytogenetic response criteria for countries where quantitative RT-PCR to determine *BCR–ABL1*^{IS} is not feasible. However, quantitative RT-PCR to determine the *BCR–ABL1*^{IS} level standardized to the International Scale became covered by the Japanese National Health Insurance in April 2015. Therefore, determination of *BCR–ABL1*^{IS} is generally possible for response assessment.

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) is performed to determine the proportion of Ph-positive cells and whether additional chromosomal abnormalities are present. *BCR–ABL1* mRNA is also quantified and BCR breakpoint and pre-treatment levels are confirmed. 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 3–6 months.
4. In the event of a marked increase in *BCR–ABL1*^{IS} or treatment failure as defined by the 2013 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 the Japanese National Health Insurance) 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 deep molecular response (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.[20] In addition, all patients who lost DMR after discontinuation of imatinib regained DMR after resuming imatinib. Whether or not TKI therapy can be discontinued in patients who achieve DMR must be further validated in clinical trials,[21] and Version 3.2020 of the NCCN guidelines discuss the importance of criteria that must be

met when discontinuing TKIs outside a clinical trial and of periodic monitoring after discontinuation.[22]

Ph-negative myeloproliferative neoplasms (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 3–8% of patients with ET and PMF, and mutations in *calreticulin* (*CALR*) are observed in 20–30% of patients with ET and PMF and cause chaotic proliferation of blood cells.

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, 4–8 in ET, and 2.23 in PMF, and is a major cause of death in PV and ET in particular. MPNs also transform to 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)[23], but median survival for PMF is a poor 3.8 years.[24] 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[25]

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).

Summary of treatments for PV

1. These treatments are performed for patients with general risk factors for thrombosis such as hypertension, dyslipidemia, obesity, and diabetes.
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. In phlebotomy, between 200 and 400 mL of blood are removed at a pace of one or two sessions per month while monitoring hemodynamic parameters such as blood pressure and pulse rate with the goal of reducing hematocrit to 45% or less. More frequent phlebotomy sessions at a lower volume (100–200 mL) are recommended for elderly patients and patients with cardiovascular disease to avoid rapid hemodynamic changes. If not contraindicated for reasons such as hemorrhage or gastrointestinal symptoms, treatment with 75–100 mg/day of oral aspirin is selected.

Hydroxyurea is the drug of choice for cytoreductive therapy. Ruxolitinib is used in patients intolerant or resistant to hydroxyurea.[26] As hydroxyurea is teratogenic, interferon alpha is sometimes considered for patients who are pregnant or planning to become pregnant. Interferon alpha should also be considered for patients younger than 40 years because the risk of secondary cancer with long-term use of hydroxyurea has not been completely ruled out.

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

Table 5 Classification of thrombosis risk in patients with PV

Author	Prognostic factors	Risk classification
Barbui T, et al. (J Clin Oncol. 2011; 29:761)	Age < 60 years and no history of thrombosis	Low-risk group
	Age ≥ 60 years or history of thrombosis	High-risk group
Tefferi A, et al. (Semin Hematol. 2005; 42:206)	Meets all of the following criteria: Age < 60 years No history of thrombosis Platelet count < 1,500,000/μL No risk factors for cardiovascular disease (smoker, hypertension, congestive heart failure)	Low-risk group
	Not classified into low or high-risk group	Intermediate-risk group
	Age ≥ 60 years or history of thrombosis	High-risk group

Table 6 Classification of thrombosis risk in patients with ET

Author	Prognostic factors		Risk classification
Barbui T, et al. (J Clin Oncol. 2011; 29:761)	Age < 60 years and no history of thrombosis		Low-risk group
	Age ≥ 60 years or history of thrombosis		High-risk group
Ruggeri M, et al. (Br J Haematol.1998; 103:772)	Age < 60 years, no history of thrombosis, and platelet count < 1,500,000/μL		Low-risk group
	Age ≥ 60 years, history of thrombosis, or platelet count ≥ 1,500,000/μL		High-risk group
Barbui T, et al. (Blood Cancer J. 2015; 5:e369)	Age < 60 years and no history of thrombosis	No *JAK2* mutation	Very low-risk group
		JAK2 mutation	Low-risk group
	Age ≥ 60 years, no history of thrombosis, and no *JAK2* mutation		Intermediate-risk group
	Age ≥ 60 years and *JAK2* mutation		High-risk group
	History of thrombosis		

as being at high risk for thrombosis.[27] A risk classification system that incorporates *JAK2* mutations was recently proposed (Table 6).[28] There is no consensus regarding whether or not WBC count, platelet count, or cardiovascular risk factors such as 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).[29,30]

Summary of treatments for ET

1. Patients at low risk of thrombosis should be observed periodically. Treatment with myelosuppressive or platelet-reducing drugs is unnecessary.[26] Treatment with low-dose aspirin is generally unnecessary as well, but aspirin can be considered for patients with *JAK2* mutations, cardiovascular risk factors (smoking, hypertension, dyslipidemia, and diabetes), or symptoms suggestive of microvascular embolism or thrombosis.[31]
2. Patients at high risk of thrombosis should be treated with a combination of low-dose aspirin and cytoreductive therapy to prevent thromboembolic complications.[32,33]

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. 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. Patients with a platelet count less than 1,000,000/μL can sometimes have a low vWF level as well,[34] and thus testing for vWF:RCo is advisable for all patients with a bleeding tendency regardless of platelet count. Hydroxyurea and anagrelide are options for cytoreductive therapy.[33,35] The age of onset of ET is younger than that of PV, and it is slightly more common in women. Consequently, treatment of patients who are pregnant or planning to become pregnant can be an issue, and interferon alpha should be considered in such patients (not covered by the Japanese National Health Insurance).

Table 7 Risk classification for predicting survival in patients with ET[28,29]

Author	Prognostic factors	Risk classification	Median survival (years)
Wolanskyj AP, et al. (Mayo Clin Proc. 2006; 81:159)	Age < 60 years and WBC count < 15,000/μL	Low-risk group	25.3
	Age ≥ 60 years or WBC count ≥ 15,000/μL	Intermediate-risk group	16.9
	Age ≥ 60 years and WBC count ≥ 15,000/μL	High-risk group	10.3
Passamonti F, et al. (Blood. 2012; 120:1197)	Age ≥ 60 years (2), WBC count ≥ 11,000/μL (1), History of thrombosis (1)	Low-risk group (0) Intermediate-risk group (1, 2) High-risk group (3, 4)	Not reached 24.5 13.8

Primary myelofibrosis (PMF)

Prognostic classification for PMF

Three versions of the International Prognostic Scoring System (IPSS) are in use: the original IPSS, which comprises the 5 prognostic factors of age (> 65 years), clinical symptoms (e.g., weight loss, night sweats, and fever), hemoglobin level (< 10 g/dL), WBC count at diagnosis (> 25,000/μL), and peripheral blast percentage (≥ 1%);[36] the Dynamic IPSS (DIPSS), which assigns different weights to these 5 factors;[37] and the DIPSS Plus, which adds cytogenetic abnormalities, platelet count, and transfusion dependence to the DIPSS (Table 8).[38] 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. Each system is useful for prediction of prognosis and is used for treatment selection.

Summary of treatments for PMF

1. Treatment for Low- and Int-1-risk groups: As survival in patients without clinical symptoms or anemia is over 10 years, observation is currently the best approach. If symptoms are present, applicable symptomatic treatment should be performed [refer to (3) and (4)].
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 if possible. Approximately 50% of patients who undergo allo-HSCT achieve long-term survival. Patients not eligible for allo-HSCT are treated with ruxolitinib. Ruxolitinib can be expected to reduce splenomegaly and symptoms, as well as to improve the survival prognosis.[39,40]
3. Anemia is treated with RBC transfusions or anabolic steroids. Danazol 600 mg/day is commonly used for anabolic steroid therapy outside Japan, but methenolone acetate is often used in Japan.[41]
4. Hydroxyurea, splenectomy, and radiotherapy have been shown to be effective in treating abdominal pain and other symptoms associated with splenomegaly. If hydroxyurea is started at a dose of 1000 mg/day, it will reduce the size of the spleen in about 40% of patients.[42] The main adverse event is myelosuppression. Splenic irradiation is also effective, but only temporarily, and

Table 8 Prognostic model for PMF

Prognostic model	Unfavorable prognostic factors (score)	Prognostic evaluation		
		Total score	Risk classification	Median survival (years)
IPSS (Blood. 2009; 113:2895)	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 (Blood. 2010; 115:1703)	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 (J Clin Oncol. 2011; 29: 392)	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

requires that patients be carefully monitored for severe cytopenia and infection.[43]

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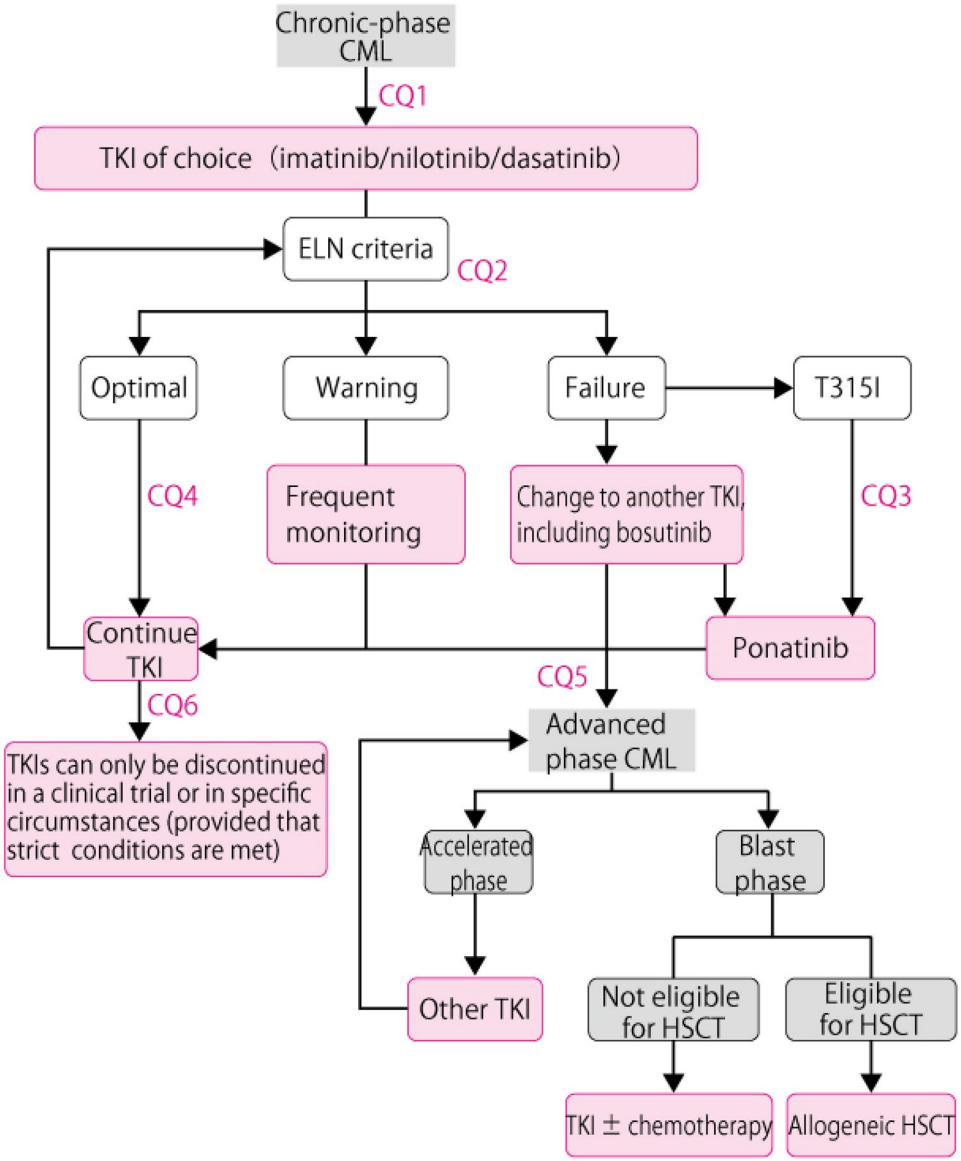
Algorithms

Algorithm for CML



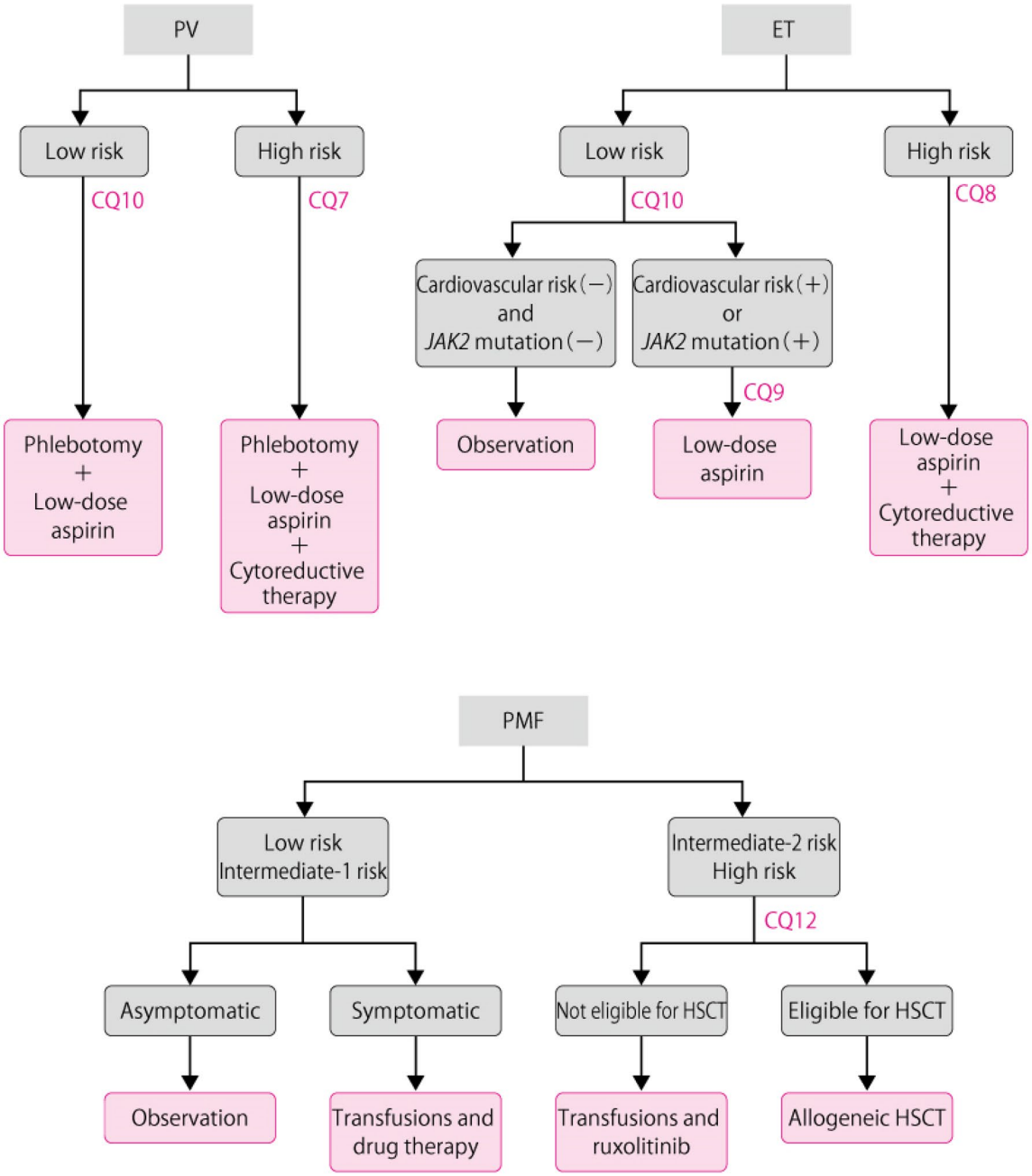
Tyrosine kinase inhibitors (TKIs) are currently the key drug for CML treatment. CML-CP is treated with a TKI (imatinib, nilotinib, or dasatinib) (CQ1). If an optimal response is achieved after treatment is started, treatment is continued. In case of warning, frequent monitoring is performed (CQ2). In case of failure, treatment is switched from imatinib to another TKI, from nilotinib to dasatinib or bosutinib, or from dasatinib to nilotinib or bosutinib. Point mutation analysis informs drug selection in TKI-resistant patients. Ponatinib is effective in third-line therapy for patients with *ABL1* mutations including T315I, as well as patients resistant or intolerant to prior therapy (CQ3). High-risk patients should be identified and monitored to prevent cardiovascular adverse reactions associated with long-term TKI use (CQ4). CML-AP that has progressed from CML-CP is treated with a previously unused TKI, and CML-BP is treated with a TKI alone or in combination with chemotherapy for acute leukemia. Allo-HSCT is recommended in patients eligible for transplantation (CQ5). Although TFR is the new goal of CML therapy, discontinuation of TKIs should only be

attempted in a clinical trial at this point in time. However, discontinuation of TKIs can be considered for patients who have achieved DMR but face obstacles to continuing TKIs such as trying to become pregnant or experiencing late adverse reactions, as long as they meet certain criteria and are monitored periodically (CQ6).

Algorithm for MPN

The treatment approach for PV, ET, or PMF essentially consists of deciding on a treatment plan on the basis of 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. Reduction of hematocrit to less than 45% by hydroxyurea is another treatment goal for high-risk PV (CQ7). 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 in order to reduce risk of thrombosis (CQ9). 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 (CQ8). When treating pregnant patients with ET, intervention with low-dose aspirin or interferon alpha may reduce the risk of miscarriage (CQ11).

The survival prognosis of PMF 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. Observation without treatment is advisable for asymptomatic patients. Allo-HSCT should be considered for Int-2- and High-risk group patients with a suitable donor because the survival prognosis for these groups is unfavorable (CQ12). Allo-HSCT is the curative treatment option for PMF. Patients not eligible for HSCT are treated with ruxolitinib. Ruxolitinib can be expected to reduce splenomegaly and general symptoms, as well as to improve the survival prognosis.

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

Recommendation grade:
Category 1
Imatinib (400 mg once daily [QD]), nilotinib (300 mg twice daily [BID]), or dasatinib (100 mg QD) is recommended for treatment of newly diagnosed CML-CP. The three drugs have different adverse reaction profiles, and thus it is advisable to select an appropriate drug with consideration to comorbidities and other patient characteristics.

Explanation

A trial comparing TKI imatinib with combination of chemotherapy and interferon alpha (IFNα) (the IRIS trial) demonstrated the superiority of imatinib.[1] The long-term efficacy and safety of imatinib have also been shown: the 8-year overall survival (OS) rate was 85% (93% when only CML-related deaths were considered) and the 10-year OS rate was 83.3%.[2,3] Later trials compared high-dose (800 mg QD) imatinib with standard-dose (400 mg QD) imatinib but found no clear difference in efficacy between groups.[4–6] Therefore, 400 mg QD is currently a recommended dose level for imatinib therapy.

Results of phase III trials comparing the second-generation TKIs nilotinib and dasatinib against a control of imatinib have been published. Treatment with nilotinib 300 mg BID (ENESTnd trial)[7] and dasatinib 100 mg QD (DASISION trial)[8] yielded superior rates of complete cytogenetic response (CCyR) and major molecular response (MMR) at 12 months compared with imatinib 400 mg QD. Data from the past 5 years have not shown a significant difference in OS rate, but have shown a low rate of progression to AP/BP. The ENESTnd trial, but not the DASISION trial, also showed a significant decrease in CML-related mortality. The above evidence demonstrates that second-generation TKIs are superior to imatinib in efficacy.[9,10] Therefore, on the basis of the results from these prospective studies, treatment with a second-generation TKI is recommended for high-risk patients, such as those with a high Sokal score before treatment. There is no consensus regarding which TKI should be used first because no study to date has directly compared the second-generation TKIs nilotinib and dasatinib.[11] However, the frequency of cardiovascular adverse reactions over the 5-year observation period was higher with second-generation TKIs than imatinib (ischemic cardiovascular events of all grades: 12/258 patients treated with dasatinib 100 mg QD vs. 6/258 patients treated with imatinib 400 mg QD; 21/279 patients treated with nilotinib 300 mg BID vs. 6/280 patients treated with imatinib 400 mg QD).[9,10] The three TKIs have different adverse reaction profiles, and thus it is advisable to select an appropriate first-line drug with consideration to comorbidities and other patient characteristics.

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

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

Explanation

Measures conventionally used to monitor response to treatment for CML have been the percentage of Philadelphia chromosome-positive cells on cytogenetic testing of bone marrow cells by G-banding, the percentage of *BCR–ABL1* -positive cells on fluorescence in situ hybridization (FISH), and the *BCR–ABL1* mRNA copy number on quantitative reverse transcriptase polymerase chain reaction (RT-PCR). Almost all patients treated with a TKI such as imatinib achieve a molecular response (MR), and thus the 2013 ELN recommendations list quantitative RT-PCR with peripheral blood as the main method for response assessment.[1] The 2013 ELN recommendations also list cytogenetic analysis alongside quantitative RT-PCR as another option for countries where quantitative RT-PCR cannot be performed following standardized methods.[1] 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 *ABL* or another control gene and standardize that ratio to the International Scale. This figure is expressed as *BCR–ABL1*^{IS}. Quantitative RT-PCR to determine the *BCR–ABL1*^{IS} levels standardized to the International Scale became covered by the Japanese National Health Insurance in April 2015.

Subset analysis in the IRIS study showed very favorable outcomes for patients who achieved a major molecular response (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,[2–4] 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[5,6] and DASISION[7,8] 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.

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CQ 3 What is the recommended second-line therapy after a response of warning or failure according to the ELN response assessment criteria?

Recommendation grade:
Category 2A
Treatment with bosutinib or another second-generation TKI not previously used, selected with consideration to results of *ABL1* point mutation analysis, is recommended as second-line therapy for CML-CP.

Explanation

If the response to first-line therapy is warning as defined in the 2013 ELN recommendations, 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. If the response is failure as defined in the 2013 ELN recommendations, the patient is tested for *ABL1* point mutations and additional chromosomal abnormalities. The second-generation TKI (nilotinib, dasatinib, or bosutinib) as an appropriate second-line therapy is then selected depending on which *ABL1* point mutations were detected.[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%).[2] A phase III trial in which patients resistant or intolerant to imatinib were switched to dasatinib at a randomized dose of 100 mg QD, 50 mg BID, 140 mg QD, or 70 mg BID also showed favorable outcomes after 6 years of follow-up (MMR rate at Year 6: approximately 40% in each group, 6-year OS rate: ≥ 70%).[3] Bosutinib is used as a second- or third-line drug to treat CML resistant or intolerant to previously used TKIs (imatinib, nilotinib, or dasatinib). 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%).[4] A subanalysis in a phase I/II trial in which patients with CML resistant or intolerant to nilotinib or dasatinib after switching from imatinib switched to bosutinib also showed favorable outcomes (cumulative CCyR rate: 24%, 2-year OS rate: 83%).[5]

Ponatinib has also been shown to be effective as third-line therapy for TKI-resistant CML. Switching to ponatinib yielded a CCyR rate of 46% and an MMR rate of 34% in a phase II trial in patients with TKI-resistant/intolerant CML heavily pretreated with second-generation TKIs and patients with the T315I mutation.[6]

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CQ 4 What is the recommended method for monitoring for adverse reactions during long-term 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.

Explanation

Serious cardiovascular events (ischemic heart disease, pulmonary arterial hypertension [PAH], peripheral arterial occlusive disease [PAOD], and cerebral infarction) are known to occur during long-term treatment with second-generation TKIs. Over the 5-year observation periods in the ENESTnd and DASISION trials, the incidence of cardiovascular adverse reactions was higher with second-generation TKIs than the control of imatinib (ischemic cardiovascular events of all grades: 21/279 patients treated with nilotinib 300 mg BID vs. 6/280 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] 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.[3]

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).[4] 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.[5]

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.[6] 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.[7] 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, monitoring for PAH periodically is recommended for all patients. Periodic BNP testing and Doppler ultrasound are useful in screening and monitoring for PAH.[7] PAH is treated by discontinuation of dasatinib, and has even been shown to be reversible if treated early.[8]

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CQ 5 Are TKIs recommended for treating advanced-phase CML (AP and BP)?

Recommendation grade:
Category 2A
Nilotinib 400 mg BID or dasatinib 70 mg BID is recommended for newly diagnosed CML-AP, and a TKI not previously used, including bosutinib and ponatinib, is recommended for CML-AP previously treated with a TKI. Allo-HSCT should be considered if an optimal response is not obtained with TKI therapy.

Recommendation grade:
Category 2A
For CML-BP, allo-HSCT is recommended if at all possible once the maximum response is achieved with a TKI selected based on sensitivity, used either alone or in combination with chemotherapy.

Explanation

Imatinib has limited efficacy for advanced-phase CML.[1,2] Single-arm prospective trials in patients with imatinib-resistant AP/BP patients demonstrated the clinical efficacy of the second-generation TKIs dasatinib,[3,4] nilotinib,[5,6] and bosutinib[7] and the third-generation TKI ponatinib.[8]

Point mutation analysis is recommended for patients with CML that has become advanced-phase on TKI therapy because these patients sometimes have *ABL1* point mutations that confer TKI resistance. A different TKI from that used previously is selected, and if any point mutations are detected, selection is based on the TKI sensitivity profile of those mutations.[9]

Patients with untreated de novo CML-AP are naïve to TKIs, and thus expected to be more sensitive to TKIs than patients with previously treated CML-AP. An analysis of 51 patients with de novo CML-AP showed that 36 months of treatment with a second-generation TKI yielded favorable outcomes (OS rate: 95%).[10]

When treating CML-BC, a TKI to which mutations identified by *ABL1* point mutation analysis are sensitive is selected. Combination with chemotherapy can be expected to improve response to treatment. An ALL-style chemotherapy regimen that includes vincristine and a steroid is used for lymphoid BP,[11] whereas an AML-style regimen that includes cytarabine is used for myeloid BP.[12] However, as treatment outcomes of TKIs alone or in combination with chemotherapy are not satisfactory, allo-HSCT is strongly recommended for eligible patients. A German CML group found that the 3-year OS rate after allo-HSCT for advanced-phase CML was 59%, indicating that allo-HSCT can be expected to yield more favorable results than TKIs alone or in combination with chemotherapy.[13] 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.[14]

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CQ 6 Is it recommended to discontinue TKIs after achieving DMR if MRD is not detected?

Recommendation grade:
Category 4
Until criteria for safely stopping TKI therapy after achieving DMR are established, TKIs should not be discontinued outside of a clinical trial.

Recommendation grade:
Category 2A
However, discontinuation of TKIs can be considered in special circumstances (e.g., when the patient is trying to become pregnant or is experiencing a serious adverse reaction) provided that the patient consents to treatment fully informed that the possibility of blast crisis cannot be completely ruled out, that MRD monitoring by quantitative PCR is performed periodically, and that TKI therapy is resumed as soon as possible if MMR is lost.

Explanation

Treatment-free remission (TFR) refers to maintenance of remission without molecular relapse after discontinuation of TKIs. Studies such as the STIM trial showed that approximately 40–60% of patients formerly on long-term imatinib therapy can achieve TFR.[1–3] Molecular relapse most often occurs within 6 months of discontinuation, and another deep molecular response (DMR) is achieved by resuming imatinib in that event.[1–3] In the Japanese JALSG STIM213 trial, the 3-year TFR rate among patients formerly on long-term imatinib therapy (n = 68) was 64.6%, and all patients with molecular relapse achieved subsequent remission after resuming imatinib.[4] The criteria that must be met to discontinue imatinib (which were also applied in the JALSG STIM213 study) are achievement of a DMR deeper than MR[4,5] after at least 3 years of treatment with imatinib and maintenance of that DMR for at least 2 years.[1–4] The DADI trial, which investigated the safety and efficacy of

discontinuation of dasatinib after switching to dasatinib from prior therapy including imatinib due to resistance or intolerance, set maintenance of DMR for at least 1 year as the condition for discontinuing dasatinib, and 30 of 63 patients (49%) were maintaining DMR as of 6 months after discontinuation.[5] Progression has only been detected in 1 patient to date in any clinical trial with a strict protocol of monitoring for MRD and resuming treatment in case of MRD.[2] Although achievement of TFR is undoubtedly becoming the treatment goal for the near future because it also reduces medical expenses by avoiding overtreatment and late toxicity associated with long-term treatment, TKIs should not be discontinued outside of a clinical trial until criteria for safely stopping TKI therapy are established in a large trial such as the EURO-SKI trial.

However, discontinuation of TKIs can be considered 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. Patients should avoid unplanned pregnancy,[6] and must consent to suspending TKI therapy fully informed of the risk of blast crisis in the case of a planned pregnancy. Discontinuation of TKI therapy can be considered in the case of a planned pregnancy provided that the patient meets discontinuation criteria such as those in the STIM trial (treated with TKIs for at least 3 years and maintained DMR deeper than MR$^{4.5}$ for at least 2 years). Therefore, switching to a new TKI must be considered for patients with only an optimal response who have not achieved DMR. In one randomized controlled trial (ENESTcmr) in which patients who achieved a CCyR but not DMR after at least 2 years of imatinib therapy were either switched to nilotinib 400 mg BID or continued imatinib (400/600 mg QD), switching to nilotinib yielded a significantly higher 24-month DMR rate (defined as confirmed undetectable *BCR–ABL1* in this study) (22.1% vs. 8.7%, $p = 0.0087$).[7] Switching to interferon alpha is also an option to consider for pregnant patients who do not meet TKI discontinuation criteria and patients who lost MMR after TKI discontinuation. TKI exposure should be avoided during the first trimester, but resumption of TKI therapy can be considered during the second and third trimesters if absolutely necessary.[6]

Version 3.2020 of the NCCN guidelines discuss the importance of periodic monitoring after discontinuation when discontinuing TKIs outside a clinical trial. In a Japanese clinical trial of TKI discontinuation conducted by the JALSG, safe discontinuation of TKIs was achieved by periodically monitoring *BCR–ABL1* levels by quantitative PCR after discontinuation (at least monthly for the first 6 months, once every 2 months for the subsequent 6 months, and then once every 3 months thereafter) and resuming treatment as soon as possible if MMR was lost.[4] If discontinuation of TKI therapy must be considered in routine care, it is essential to follow clinical trial protocols for periodic monitoring after discontinuation and to resume treatment as soon as possible if MMR is lost to avoid unexpected blast crisis.

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CQ 7 Is it recommended to set target hematocrit after phlebotomy in patients with PV at 45%?

Recommendation grade:
Category 1
Target hematocrit of 45% after phlebotomy should be pursued.

Explanation

The objectives of treatment for PV are to correct impaired circulation due to increased RBCs and to prevent thrombosis and hemorrhage. The publication of a study showing that reducing hematocrit to 45% or lower decreases the incidence of thrombosis resulted in the widespread recommendation to reduce hematocrit to 45% or lower by phlebotomy in patients with PV.[1] A small retrospective study found that the incidence of thrombosis increased and the OS rate decreased when hematocrit exceeded 48%.[2]

One prospective observational study investigating target hematocrit for PV in patients who received cytoreductive therapy such as aspirin, phlebotomy, or hydroxyurea found that thrombosis risk and OS rate were comparable between patients with hematocrit levels of 55% or lower and those with levels 45% or lower.[3] In contrast, a prospective randomized controlled trial in 365 patients with PV, including 245 high-risk patients, showed that treatment aiming for a hematocrit target of less than 45% (low hematocrit group) reduced deaths from cardiovascular disease and major thrombosis compared with treatment aiming for a target between 45 and 50% (high hematocrit group).[4] However, about half of patients were receiving hydroxyurea along with phlebotomy, and the low hematocrit group had not only a lower hematocrit level but also a lower WBC count than the high hematocrit group. A reduced WBC count is also known to reduce the frequency of thrombosis, and thus it is currently unknown whether the preventive effect against thrombosis is attributable purely to reducing hematocrit, or rather to reducing both hematocrit and WBC count by hematocrit-reducing therapy. Whichever the case, reduction of hematocrit to less than 45% by phlebotomy or hydroxyurea in addition to aspirin is the recommended target for high-risk PV. However, whether or not this approach is directly applicable to Japanese patients must be investigated because all studies to date have been in Western patients.

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CQ 8 What are the recommended cytoreductive therapy drugs for high-risk ET patients?

Recommendation grade:
Category 1
Both hydroxyurea and anagrelide are useful in preventing arteriovenous thrombosis and serious hemorrhage.

Explanation

High-risk ET patients are treated with cytoreductive therapy and antiplatelet therapy to prevent thrombosis. Hydroxyurea, anagrelide, and interferon are drug options for cytoreductive therapy. Among these, hydroxyurea is the most commonly used in cytoreductive therapy. In a randomized controlled trial, 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 randomized controlled trials. 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] Considering that ET is now typically diagnosed using the WHO classification, both hydroxyurea and anagrelide are recommended options for primary cytoreductive therapy for high-risk ET.

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CQ 9 Is aspirin recommended for low-risk ET patients with cardiovascular risk factors?

Recommendation grade:
Category 2A
Aspirin has not been shown to be beneficial in low-risk ET patients (< 60 years and no history of thrombosis). However, antiplatelet therapy (with 75-100 mg/day of low-dose aspirin) can be performed for low-risk ET patients with cardiovascular risk factors (smoking, hypertension, dyslipidemia, and diabetes) or *JAK2* mutations.

Explanation

Treatment with hydroxyurea and low-dose aspirin has been shown to significantly reduce the incidence of thrombosis in high-risk patients with ET (60 years and older or history of thrombosis).[1] However, the clinical benefit of antiplatelet therapy in low-risk ET patients (< 60 years and no history of thrombosis) is currently unknown. A retrospective analysis that compared the incidence of thrombosis between observation and antiplatelet therapy (including aspirin) in low-risk patients with ET showed that antiplatelet therapy did not prevent thrombosis.[2] However, a subanalysis restricted to patients with cardiovascular risk factors (smoking, hypertension, dyslipidemia, and diabetes) or *JAK2* mutations showed that antiplatelet therapy reduced the risk of thrombosis in that subset of low-risk ET patients. A retrospective analysis in low-risk ET patients with *CALR* mutations showed that low-dose aspirin did not reduce risk of thrombosis, and actually increased risk of hemorrhage.[3] To summarize, antiplatelet therapy can be performed for low-risk ET patients with *JAK2* mutations or cardiovascular risk factors.[2] However, the benefits of antiplatelet therapy for any other low-risk ET patients do not outweigh the risk of hemorrhage. Particular caution is necessary with low-risk patients with *CALR* mutations due to their reported increased risk of hemorrhage.[3]

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CQ 10 Is intervention with hydroxyurea recommended in younger patients with low-risk PV/ET?

Recommendation grade:
Category 4
Hydroxyurea has not been demonstrated as effective in patients younger than 60 years with low-risk PV/ET. In addition, the possibility that it may promote progression to acute leukemia or development of secondary cancer has not been ruled out. For these reasons, intervention with hydroxyurea is not recommended in patients younger than 60 years with low-risk PV/ET.

Explanation

Hydroxyurea is useful in cytoreductive therapy for PV/ET, and hydroxyurea plus low-dose aspirin is useful in preventing thrombosis and hemorrhage in high-risk patients.[1] The benefit of hydroxyurea to low-risk patients was unknown until the recent publication of results of a phase III trial comparing aspirin alone to hydroxyurea plus low-dose aspirin in patients with low-risk ET, defined as age 40–59 years, no history of thrombosis or hemorrhage, and a platelet count lower than 1,500,000/μL.[2] The primary endpoint, which was the rate of survival free from events such as arterial/venous thrombosis, serious hemorrhage, and death from thrombosis/hemorrhage, did not differ between groups. There was no significant difference in OS rate, either. Consequently, intervention with hydroxyurea is not recommended in patients with low-risk ET.

Alkylating agents such as busulfan are widely known to promote secondary cancer, and there are similar concerns regarding secondary cancer with hydroxyurea. Secondary cancers caused by chemotherapy for ET include AML/MDS as well as lymphomas such as non-Hodgkin lymphoma and non-hematologic malignancies such as lung, colorectal, renal, bladder, and prostate cancers. However, it is unknown whether treatment with single-agent hydroxyurea increases the incidence of secondary cancer compared to no treatment (11.2% vs. 7.3%).[3] Transformation to acute leukemia is known to be part of the natural course of PV/ET, and thus knowledge of whether or not a certain treatment increases the risk of transformation is a critical factor in treatment selection. A large-scale Swedish cohort study of 11,039 patients found that the rate of transformation to AML/MDS was 2.6% and that past treatment with hydroxyurea did not significantly increase risk.[4]

Hydroxyurea has never been investigated in a randomized controlled trial in newly diagnosed PV, but many oncologists choose to use hydroxyurea in patients aged 60 years and older or patients with a history of thrombosis in consideration of the risk of secondary cancer.[5] For these reasons, intervention with hydroxyurea is not recommended in younger patients with low-risk PV/ET.

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CQ 11 Are any interventions for reducing the risk of miscarriage recommended in pregnant patients with ET?

Recommendation grade:
Category 2B
Intervention with low-dose aspirin is recommended because it may reduce the risk of miscarriage.

Explanation

Miscarriage during early pregnancy is a common complication of ET in pregnant patients. Rare cases of maternal hemorrhage and thrombosis have also been reported. In the EXELS (Evaluation of Anagrelide Efficacy and Long-term Safety) trial, 54 enrolled patients with ET became pregnant and the live birth rate was 75.9%.[1] A recent prospective study from the United Kingdom reported 1 miscarriage and 1 stillbirth in 58 pregnant patients with myeloproliferative neoplasms (47 with ET), which were lower rates of miscarriage and stillbirth than previously reported.[2]

Interventions for ET in pregnant patients have not been compared against observation in a randomized controlled trial. However, a systematic review of cases of ET in pregnant patients discusses how low-dose aspirin is beneficial in pregnant patients with ET regardless of risk.[2,3] One specific independent factor that causes complications in ET in pregnant patients is *JAK2* V617F, and proactive intervention is required when the *JAK2* V617F mutation is detected.[4] It is also recommended to discontinue aspirin at 1–2 weeks before delivery and then resume treatment for 6 weeks after confirming the absence of postpartum hemorrhage.[5]

Another retrospective study showed that interferon alpha significantly reduces fetal death. The *JAK2* V617F mutation in particular is an independent predictor of miscarriage, and it is suggested that reducing platelet count using interferon alpha may prevent complications.[6] Peginterferon alpha is a particularly well-tolerated interferon drug, and was shown to yield a high rate of normal births in a case series study.[3] Low-dose aspirin plus interferon alpha (not covered by the Japanese National Health Insurance) should also be considered for high-risk patients with the *JAK2* V617F mutation. Pregnant patients with ET are known to be at risk of deep vein thrombosis, which occurs at a rate of over 3% in the postpartum period. Consequently, one study recommends use of low-molecular-weight heparin (not covered by Japanese National Health Insurance) during this period.[7]

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CQ 12 What are the recommended treatments for High- and Int-2-risk primary myelofibrosis?

Recommendation grade:
Category 2B
Allo-HSCT is recommended for younger patients who do not have any comorbidities and have a suitable donor.
Ruxolitinib is recommended for transplant-ineligible patients with splenomegaly or general symptoms.

Explanation

At present, allo-HSCT is the only curative treatment option for PMF. 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 higher and who are younger than 65 years.[1] Consequently, allo-HSCT is recommended for the patients younger than 65 years whose DIPSS risk group is Int-2 or higher. However, various issues with allo-HSCT have been noted, including that typical myeloablative conditioning has a high treatment-related mortality rate of 30–40%, and that the older age of onset results in few patients with PMF being eligible for transplantation.[2] Non-myeloablative conditioning is believed to reduce transplant-related mortality, but also increases rates of graft failure and relapse. Myeloablative and non-myeloablative conditioning have never been prospectively compared in a clinical trial, only retrospective analyses have been reported. Gupta et al. found no difference in post-transplantation relapse or survival rates between the both groups although patients who received non-myeloablative conditioning have older ages and longer disease duration.[3]

The JAK1/JAK2 inhibitor ruxolitinib is another treatment option for PMF besides allo-HSCT. Two phase III randomized controlled trials that set the proportion of patients with reduced spleen volume as the primary endpoint demonstrated that ruxolitinib was superior to placebo or conventional therapy,[4,5] and significantly reduced general symptoms as well. Results of long-term observation suggest that ruxolitinib also helps improve the OS rate.[6] No study has directly compared the survival benefit of ruxolitinib and allo-HSCT.

On the basis of the above results, allo-HSCT is recommended for younger MF patients in the High- and Int-2 risk

groups who do not have comorbidities and have a suitable donor, whereas ruxolitinib is recommended for transplant-ineligible patients with splenomegaly or general symptoms.

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