

CLINICAL PRACTICE GUIDELINES

Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up[†]

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Epidemiology

The incidence of chronic myeloid leukaemia (CML) ranges between 10 and 15 cases/10⁶/year without any major geographic or ethnic differences [1]. The median age at diagnosis ranges between 60 and 65 years in Europe, but is considerably lower in countries with a younger population. The prevalence of CML is steadily rising due to the substantial prolongation of survival that has been achieved with targeted therapy [2]. CML in children is rare; biology and treatment strategies in paediatric patients reveal specific aspects [3]. Therefore, these recommendations are primarily intended for use in adult patients.

Pathophysiology and diagnostic evaluation

CML is a disease of haemopoietic stem cells, arising from a translocation *t(9;22)(q34;q11)*, with the shortened chromosome 22, designated as Philadelphia chromosome, 22q-. The translocation leads to a juxtaposition of the *ABL1* gene from chromosome 9 and the *BCR* gene from chromosome 22, resulting in a *BCR-ABL1* fusion gene that codes for BCR-ABL1 transcripts and fusion proteins with high tyrosine kinase activity. The molecular pathogenesis of CML is well understood, but the mechanism that leads to the gene translocation is unknown [1].

Diagnosis of CML is generally straightforward. In most cases, the diagnosis can be made on the basis of a characteristic blood count and differential (excessive granulocytosis with typical left shift of granulopoiesis). Confirmation of diagnosis is obtained by the identification of the Philadelphia chromosome, 22q- or

BCR-ABL1 transcripts, or both, in peripheral blood or bone marrow (BM) cells. In ~5% of cases the Philadelphia chromosome cannot be detected and confirmation of diagnosis depends on the confirmation of the BCR-ABL1 fusion by either fluorescent *in situ* hybridisation (FISH) or by reverse transcriptase polymerase chain reaction (RT-PCR). These patients should be treated the same way as Philadelphia-positive (Ph+) patients. Therapeutic response is comparable [4]. In some patients with features of CML, no Philadelphia chromosome or BCR-ABL1 rearrangement can be detected [1]. These patients are referred to as Philadelphia-negative (Ph-) and BCR-ABL1 negative, or as atypical CML, according to the World Health Organization (WHO) classification, and represent a separate disease entity [5]. Treatment of atypical CML is beyond the scope of these guidelines.

BCR-ABL1 positive cells are genetically unstable and are prone to develop multiple and heterogeneous genomic abnormalities, resulting in the transformation of the leukaemic phenotype from chronic to acute, hence leading to the progression from chronic (CP) to accelerated (AP) and blast (BP) phases (Table 1) [5, 6]. Table 1 compares the WHO and the European LeukemiaNet (ELN) definitions of CML phases. Of note, the ELN definition has been used in almost all clinical trials assessing the efficacy of tyrosine kinase inhibitors (TKIs) and is recommended as a basis for treatment decisions.

Progression may be based on BCR-ABL1-dependent factors, e.g. point mutations of the kinase domain, associated with resistance to TKIs, or BCR-ABL1-independent factors, e.g. additional cytogenetic aberrations causing clonal evolution.

Table 1. Clinical and haematological criteria for the definition of AP and BP according to WHO [1] and ELN [2]

	Accelerated phase		Blast phase	
	WHO	ELN	WHO	ELN
Spleen	Persisting or increasing splenomegaly unresponsive to therapy	–	–	–
WBC count	Persisting or increasing WBC count ($> 10 \times 10^9/L$) unresponsive to therapy	–	–	–
Blast cells ^a	10%–19%	15%–29%	$\geq 20\%$	$\geq 30\%$
Basophils ^a	$> 20\%$	$> 20\%$	–	–
Platelet count	$> 1000 \times 10^9/L$ uncontrolled by therapy $< 100 \times 10^9/L$ unrelated to therapy	– Yes	–	–
CCA/Ph+	Any new clonal aberration during therapy Additional clonal chromosomal abnormalities in Ph cells at diagnosis that include ‘major route’ abnormalities (second Ph, trisomy 8, isochromosome 17q, trisomy 19), complex karyotype or abnormalities of 3q26.2	Present	–	–
Extramedullary involvement ^b	–	–	Present	Present
‘Provisional’ response-to-TKI criteria	Haematological resistance to the first TKI (or failure to achieve a complete haematological response ^c to the first TKI) or Any haematological, cytogenetic or molecular indications of resistance to 2 sequential TKIs or Occurrence of 2 or more mutations in BCR–ABL1 during TKI therapy			

The criteria of AP are different, reflecting the difficulty of making the diagnosis of this transitory phase. The criteria of BP differ only for the percent of blast cells. Only one of the listed criteria is sufficient for the diagnosis of AP or BP.

^aIn peripheral blood or in BM.

^bExcluding liver and spleen, including lymph nodes, skin, CNS, bone and lung.

^cComplete haematological response: WBC $< 10 \times 10^9/L$; platelet count $< 450 \times 10^9/L$, no immature granulocytes in the differential and spleen non-palpable.

AP, accelerated phase; BM, bone marrow; BP, blast phase; CCA/Ph+, clonal chromosome abnormalities in Ph+ cells; CNS, central nervous system; ELN, European LeukemiaNet; Ph, Philadelphia; TKI, tyrosine kinase inhibitor; WBC, white blood cell; WHO, World Health Organization.

BM biopsies taken at diagnosis show increased cellularity due to proliferation of the myelopoiesis in all stages of maturation with predominance of mature forms. Basophilia is common, and eosinophils may be prominent. Proportion of blasts vary; but, according to ELN recommendations [6], CP disease is associated with $< 15\%$ blasts in blood and BM. Megakaryocytes are smaller than normal with hypolobulated nuclei. Moderate to marked reticulin fibrosis is encountered in $\sim 30\%$ of cases. Pseudo-Gaucher cells and sea-blue histiocytes are usually observed. BM composition undergoes rapid changes during therapy. These consist of reduction of the granulocytic cellularity, normalisation of megakaryopoiesis, regression of fibrosis, lymphocytosis and normalisation of erythropoiesis.

The recognition of disease progression from CP to BP is relevant for prognosis and treatment. However, the clinical and morphological boundaries between these stages are sometimes vague. Immunocytology by flow cytometry and histochemistry allow accurate assessment of immature cells and distinction between myeloid (70%–80%) and lymphoid (20%–30%) blast crisis [1].

About 50% of patients with CML diagnosed in Europe are asymptomatic. The disease is frequently diagnosed after blood

tests are taken for some unrelated reason. At diagnosis, most (90%–95%) CML patients present in CP; initial BP is rare [1, 7]. The designation of an AP at diagnosis is conflicting but the term should be used during therapy. Common signs and symptoms of CML CP, when present, result from anaemia and splenomegaly. These include fatigue, weight loss, malaise and left upper quadrant fullness or pain. Rare manifestations include bleeding (associated with a low platelet count and/or platelet dysfunction), thrombosis (associated with thrombocytosis and/or marked leukocytosis), gouty arthritis (from elevated uric acid levels), retinal haemorrhages and upper gastrointestinal ulceration (from elevated histamine levels due to basophilia). Leukostatic symptoms (priapism, dyspnoea, drowsiness, loss of coordination, confusion) due to leukaemic cells sludging in the blood vessels are uncommon in CP despite white blood cell (WBC) count often exceeding $100 \times 10^9/L$. Splenomegaly is the most consistent physical sign detected in 40%–50% of cases. Hepatomegaly is less common. Extramedullary infiltration (apart from spleen and liver) is rare. Headaches, bone pain, arthralgias, pain from splenic infarction and fever are more frequent with CML transformation [7].

Table 2. Recommendations for diagnostic work-up, assessment of response and monitoring

	Baseline (diagnostic work-up)	To assess the response	To monitor the response and the treatment
Blood counts and differential	Yes	Every 15 days until a CHR without significant cytopaenias has been achieved	Every 3 months
BM, cytology	Yes	No	No
BM, karyotype	Yes	At 3 and 6 months	Then every 6 months until CCyR has been achieved
Blood, iFISH	No	No	Only if cytogenetics of BM metaphases cannot be analysed or is normal and molecular response cannot be assessed
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, qRT-PCR (quantitative, BCR-ABL %)	No	Every 3 months	Every 4–6 weeks in first year after treatment discontinuation
Mutational analysis	Only in AP or BP	No	Only in the case of failure

AP, accelerated phase; BM, bone marrow; BP, blast phase; CCyR, complete cytogenetic response; CHR, complete haematological response; iFISH, interphase fluorescent *in situ* hybridisation; qRT-PCR: quantitative RT-PCR; RT-PCR, reverse transcriptase polymerase chain reaction.

On TKI therapy, most patients restore normal haematopoiesis. Transient cytopaenias occur due to delayed recovery of normal haematopoiesis but good efficacy against leukaemia. CML AP might present with non-specific symptoms, worsening anaemia, splenomegaly and organ infiltration; CML BP presents as an acute leukaemia with worsening constitutional symptoms, bleeding, fever and infections.

Diagnosis must be confirmed by cytogenetics showing $t(9;22)(q34;q11)$ and by multiplex RT-PCR showing BCR-ABL1 transcripts. In rare cases, BCR-ABL1 juxtaposition can be determined by interphase FISH (iFISH) of blood cells, using dual colour dual fusion probes that allow the detection of BCR-ABL1+ nuclei. Cytogenetic assessment is required because it is necessary to detect additional chromosome abnormalities.

Qualitative multiplex RT-PCR is carried out on blood or BM RNA. It identifies the transcript type, either typical e14a2 or e13a2 (also known as b3a2 and b2a2) or atypical variants. Determination of the transcript type is crucial for later monitoring, in particular for the accurate assessment of molecular response.

Quantitative RT-PCR (qRT-PCR) measuring BCR-ABL1 transcripts level as BCR-ABL1 % on the International Scale (IS) and BCR-ABL1 mutation analysis are not required at baseline. Baseline mutational analysis in patients with newly diagnosed CML CP is not advised, as this has not been proven to provide information on optimal treatment selection and to predict therapeutic outcome.

Recommendations for the baseline diagnostic work-up are summarised in Table 2 [V, A].

Staging and risk assessment

The relative risk of a patient with CML can be calculated using simple clinical and haematological data provided that they were collected before any treatment. The Sokal score has been developed in the chemotherapy era and the Euro score in the interferon alpha (IFN α) era, with survival as the endpoint for both. The chance of

achieving a complete cytogenetic response (CCyR) after 18 months of TKI therapy can be estimated with the European Treatment and Outcome Study (EUTOS) score. The EUTOS Long-Term Survival (ELTS) score for patients on TKI therapy considers CML-related deaths only (Table 3) [III, A] [8]. Despite randomised first-line trials employing different scores, the intrinsic risk of early acceleration or blast crisis in low-risk patients is low with all available TKIs.

Major route cytogenetic aberrations (+8, iso(17-q), +19, +22q-), chromosome 3 aberrations and BM fibrosis at diagnosis have been associated with an unfavourable outcome after imatinib therapy [9] and are considered warning signs.

First-line management of chronic phase CML

The three commercially available TKIs for the front-line treatment of CML are imatinib, dasatinib and nilotinib (Figure 1); options for first-line therapy in CML CP are imatinib 400–800 mg/day, nilotinib 300 mg twice daily or dasatinib 100 mg/day. TKI selection should be based on treatment goals, age and comorbidities and should take into consideration the adverse event (AE) profile of the available drugs. With all three TKIs, overall survival (OS) after 5 years is 85%–95% [I, A]. So far, no significant survival difference between imatinib and second generation inhibitors has been observed.

Imatinib mesylate was the first TKI to receive approval for the treatment of patients with CML CP. It acts via competitive inhibition at the adenosine triphosphate (ATP)-binding site of the BCR-ABL1 oncoprotein, which results in the inhibition of phosphorylation of proteins involved in cell signal transduction. It efficiently inhibits the BCR-ABL1 kinase, but, among others, also blocks the platelet-derived growth factor (PDGF) receptors and the KIT tyrosine kinase.

The International Randomised Study of Interferon and STI571 (IRIS) study is considered a landmark clinical trial for CML treatment with TKIs. A total of 1106 patients in CML CP were randomised to

Table 3. Calculation of the relative risk of a patient with CML using clinical and haematological data obtained before any treatment []

	Sokal	EURO	EUTOS	ELTS
Age (years)	0.116 (age - 43.4)	0.666 when age > 50	N/A	$0.0025 \times (\text{age}/10)^3$
Spleen size ^a (cm)	$0.345 \times (\text{spleen} - 7.51)$	$0.042 \times \text{spleen}$	$4 \times \text{spleen}$	$0.0615 \times \text{spleen}$
Platelet count ($\times 10^9/\text{L}$)	$0.188 \times [(\text{platelets}/700)^2 - 0.563]$	1.0956 when platelets ≥ 1500	N/A	$0.4104 \times (\text{platelets}/1000)^{-0.5}$
Blood blast cells (%)	$0.887 \times (\text{blast cells} - 2.10)$	$0.0584 \times \text{blast cells}$	N/A	$0.1052 \times \text{blast cells}$
Blood basophils (%)	N/A	0.20399 when basophils > 3%	$7 \times \text{basophils}$	
Blood eosinophils (%)	N/A	$0.0413 \times \text{eosinophils}$	N/A	
Relative risk	Exponential of the total	Total $\times 1000$	Total	Total
Low	< 0.8	≤ 780	≥ 87	≤ 1.5680
Intermediate	0.8–1.2	781–1480	N/A	1.5680–2.2185
High	≥ 1.2	≥ 1480	≥ 87	≥ 2.2185
Endpoint	Survival	Survival	CCyR	CML-specific survival

^aSpleen size is measured by manual palpation and expressed as maximum distance perpendicular from costal margin.

CCyR, complete cytogenetic response; CML, chronic myeloid leukaemia; ELTS, EUTOS Long-Term Survival; EUTOS, European Treatment and Outcome Study; N/A, not applicable.

receive imatinib 400 mg/day or IFN α plus low-dose cytarabine. After a median follow-up of 19 months, outcomes for patients receiving imatinib were significantly better than in those treated with IFN α plus cytarabine, notably the rates of CCyR (74% versus 9%, $P < 0.001$), and freedom from progression to AP or BP at 12 months (99% versus 93%, $P < 0.001$) [10]. Responses to imatinib were also durable: in a 10-year follow-up of the IRIS study, the estimated event-free survival rate was 79.6%, and the OS rate was 83.3% [11].

High-dose imatinib and combination with IFN α

Other strategies for front-line therapy include using higher doses of imatinib or combining a TKI with an additional agent, such as IFN α . In the German CML IV study, patients with tolerance- and response-adapted high-dose imatinib achieved deep molecular remission (DMR) more quickly than patients on standard-dose imatinib [12, 13]. A recent meta-analysis revealed an advantage of high-dose imatinib with regard to achievement of major molecular response (MMR) at 12 months of therapy [14].

IFN α has re-emerged as an interesting therapeutic option in CML with the advent of PEGylated formulations (with polyethylene glycol PEG) requiring less frequent administration, improved efficacy and tolerability. In the French SPIRIT trial, patients were randomised to receive imatinib 400 or 600 mg/day, imatinib 400 mg/day plus PEG-IFN α -2a, or imatinib 400 mg/day plus subcutaneous cytarabine. At 12 months, rates of CCyR were similar among the 4 groups. The imatinib plus PEG-IFN α -2a-treated group obtained higher rates of MMR and DMR [15]. PEGylated IFN α in combination with dasatinib appeared to improve molecular response rates in a single-armed phase II study with historical controls [16]. IFN α maintenance after TKI therapy may help to bridge to treatment-free remission (TFR) [17]. In all, despite lack of registration, PEGylated IFN α is promising as an agent to increase the proportion of patients that may discontinue (see Table 4), but must still be considered investigational.

Dasatinib is an oral, second generation multikinase TKI that is 350 times more potent than imatinib *in vitro* and inhibits multiple kinases including Src-family members. The DASISION trial

was a phase III randomised study comparing dasatinib 100 mg/day to imatinib 400 mg/day in 519 newly diagnosed patients with CML. Patients assigned to dasatinib achieved confirmed CCyR at 12 months more often than those on imatinib (77% versus 66%, $P < 0.007$). A 5-year follow-up showed that dasatinib induced more rapid and deeper responses at early time points compared with imatinib. At 3 months, a higher proportion of patients treated with dasatinib achieved BCR-ABL1 transcripts <10% on the IS (84% versus 64%, $P < 0.0001$). Meeting this threshold in either arm predicted for better progression-free survival (PFS) and OS. Transformations to CML AP or CML BP were fewer in patients treated with dasatinib versus imatinib at 5 years (4.6% versus 7.3%) [18, 19].

Nilotinib is a structural analogue of imatinib. Compared with imatinib, the *in vitro* affinity for the BCR-ABL1 ATP-binding site is 30- to 50-fold higher. In the ENESTnd study, two doses of nilotinib (300 or 400 mg twice daily) were compared with imatinib 400 mg/day. The primary endpoint, MMR rate at 12 months, was achieved at higher rates for both doses of nilotinib compared with imatinib (44% and 43% versus 22%, $P < 0.001$). The cumulative incidence of CCyR by 24 months was 87% and 85% with nilotinib 300 mg twice daily, and 400 mg twice daily, respectively, and 77% with imatinib 400 mg/day ($P < 0.001$). By 5 years, the cumulative incidences of MMR by 60 months were 77%, 77% and 60%, respectively ($P < 0.0001$). The incidences of DMR with BCR-ABL1 transcripts [IS] $\leq 0.0032\%$ (equivalent to a 4.5 log reduction) by 72 months were 56%, 55% and 33%, respectively ($P < 0.0001$). The incidences of transformation to AP or BP were 3.9%, 2.1%, and 7.4%, respectively ($P = 0.06$ and 0.003 , respectively). The estimated 5-year survival rates were 94%, 96%, and 92%, respectively. While nilotinib was superior to imatinib across all Sokal score categories in inducing higher rates of CCyR and MMR, the advantage in reducing the rates of transformation was more pronounced in patients with intermediate- and high-Sokal-risk CML. The rates of transformations were 1%, 1% or 0% in Sokal low-risk patients treated with nilotinib 300 mg twice daily, 400 mg twice daily or imatinib 400 mg/day. The rates were

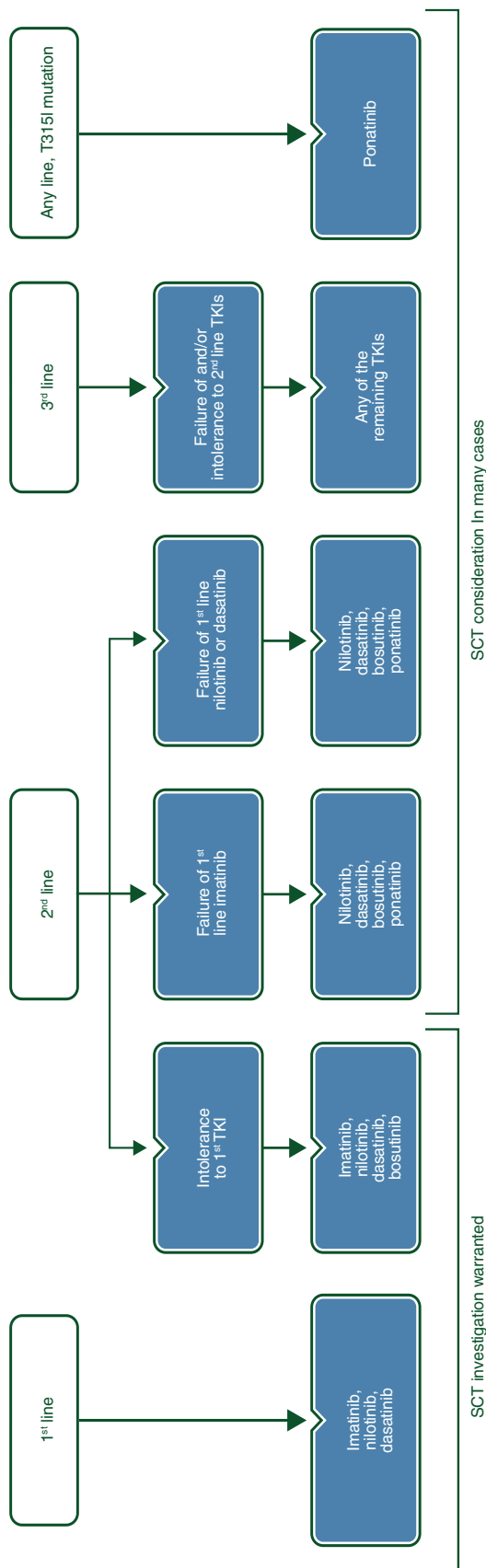


Figure 1. Treatment options for chronic phase CML patients. CML, chronic myeloid leukaemia; SCT, stem cell transplantation; TKI, tyrosine kinase inhibitor.

Table 4. Minimum requirements for treatment-free remission [40]

Institutional requirements for safe supervision of TFR:

1. Availability of high quality internationally standardised, accurate, sensitive qRT-PCR laboratory
2. Rapid turn-around of PCR test results—within 4 weeks
3. Capacity to provide PCR tests every 4–6 weeks, when required
4. Structured follow-up established to enable rapid intervention if BCR-ABL1 is rising

Green criteria, which support treatment-free remission:

1. Institutional criteria met
2. Sokal-Score at diagnosis non-high
3. Typical b2a2- or b3a2-BCR-ABL1 transcripts, or atypical transcripts which can be quantified over a 4.5 log dynamic range
4. Chronic phase disease
5. Optimal response to first-line therapy
6. Duration of TKI therapy > 5 years
7. MR^{4.5} reached
8. Duration of deep molecular response (MR⁴ or MR^{4.5}) (standardised lab) > 2 years

MR, molecular response; PCR, polymerase chain reaction; qRT-PCR, quantitative reverse transcriptase PCR; TFR, treatment-free remission; TKI, tyrosine kinase inhibitor.

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2%, 1% or 10% among patients with intermediate Sokal risk and 9%, 5% or 11% among patients with high Sokal risk [20, 21].

Selecting first-line therapy

Therapy goals should be discussed with the patient and defined before the selection of the first-line drug. With all three TKIs licensed for first-line therapy, survival chances are similar [I, A]. However, the chance to achieve DMR with an option to discontinue therapy is higher with dasatinib and nilotinib as compared with imatinib [V, C]. This may be particularly relevant for young female patients with a wish to become pregnant and for all patients with a long life expectancy. Risk of transformation to AP and BP is lower in Sokal non-low-risk patients using dasatinib or nilotinib [I, A]. The use of generic imatinib may be considered to reduce cost of therapy substantially, but also for its safety profile, particularly in elderly patients [22]. In some countries imatinib may be mandatory for first-line use on cost-effectiveness/reimbursement grounds. However, many different forms of generic imatinib are being commercialised worldwide and precise information on the tolerance and efficacy of each of these different compounds are rare. Recent results from a randomised study (ClinicalTrials.gov Identifier: NCT02130557) suggest the alternative use of bosutinib 400 mg/day as first-line therapy for CP CML patients, but registration is pending.

Comorbidities are the major cause of death in CML patients and may be aggravated by AEs [23]. Therefore, patient's age, comorbidities and the specific TKI toxicity profile should be considered [V, B]. For patients at risk of developing pleural effusions (existing lung disorders or uncontrolled hypertension), dasatinib should be avoided. Pulmonary arterial hypertension (PAH) is a rare complication of dasatinib, and patients with pre-existing

PAH may be considered for alternative TKIs in the front-line setting. Dasatinib also inhibits platelet function, and patients taking concomitant anticoagulants may be at an increased risk of haemorrhagic complications [V, B].

Nilotinib has been associated with hyperglycaemia; caution should be exercised in patients with uncontrolled diabetes mellitus (DM) when initiating therapy. Patients should take nilotinib on an empty stomach to avoid excess drug exposure with fat-containing food. Nilotinib has also been associated with vaso-spastic and vaso-occlusive vascular events, such as ischaemic heart disease, ischaemic cerebrovascular events and peripheral artery occlusive disease [I, C]. Nilotinib use should be prescribed with caution in patients with risk factors such as DM or coronary, cerebrovascular or peripheral arterial disease. A thorough intervention against cardiovascular risk factors such as smoking, hyperlipidaemia, hypertension and DM is warranted [V, A].

Imatinib causes persisting but mostly mild to moderate side-effects with significant impact on quality of life (QoL) including weight gain, fatigue, peripheral and periorbital oedema bone and muscle aches, nausea and others. All available TKIs may prolong the QT interval; thus, potassium and magnesium should be repleted to appropriate serum levels before starting therapy [V, B].

Hydroxyurea (40 mg/kg body weight/day) may be used as initial therapy before confirmation of the BCR-ABL1 fusion and immediate need for therapy because of high leukocyte counts or clinical symptoms. TKI therapy should be commenced immediately after confirmation of BCR-ABL1 positivity. It is recommended to taper the hydroxyurea dose before its discontinuation.

To avoid tumour lysis syndrome, 2.5–3 L fluid intake is recommended per day considering the individual cardiac and/or renal situation. Sodium bicarbonate may be used to set the urine pH to 6.4–6.8 for optimal uric acid clearance. Allopurinol may increase the risk of xanthine accumulation with renal failure and should therefore be restricted to patients with symptomatic hyperuricaemia.

The recommendations on follow-up therapy are based on the assessment of the response (Table 5) and on the definition of the response (Table 6). The response to TKIs can be classified as optimal, meaning that continuing treatment survival is predicted to be normal or close to normal; and failure, meaning that treatment must be switched to an alternative TKI, or allogeneic stem cell transplantation (alloSCT) should be considered. Between optimal and failure, there is a grey zone that is defined as ‘warning’, meaning that the response must be monitored more carefully and that the patient may be eligible for potentially better treatments [V, A] [6].

The choice of treatment, particularly the decision of moving from one treatment to another, strongly depends on the response to treatment, i.e. on the degree of the cytogenetic response, molecular response and on the detection of BCR-ABL1 kinase domain mutations.

Cytogenetic monitoring

Cytogenetic monitoring must be carried out by analysis of marrow cell metaphases, reporting the proportion of Ph+ metaphases of at least 20 metaphases analysed. The cytogenetic response is defined as complete (CCyR) with 0% Ph+ metaphases, partial (PCyR) with 1%–35% Ph+ metaphases, minor with 36%–65% Ph+ metaphases, minimal with 66%–95% Ph+ metaphases and none if > 95% of metaphases are still Ph+. iFISH data cannot be used to calculate the cytogenetic response categories.

Table 5. Assessment of response

CHR (Complete haematological response)

WBC count < 10 × 10⁹/L
No immature granulocytes
Basophils < 5%
Platelet count < 450 × 10⁹/L
Spleen non-palpable

Cytogenetic response (CyR)

Complete CyR	No Ph+ metaphases by CBA, or < 1% BCR-ABL+ nuclei by iFISH out of ≥ 200 cells
Partial CyR	1%–35% Ph+ metaphases by CBA
Minor CyR	36%–65% Ph+ metaphases by CBA
Minimal CyR	66%–95% Ph+ metaphases by CBA
No CyR	> 95% Ph+ metaphases by CBA

Molecular response (MR)

Major MR (MMR)	BCR-ABL transcript level ≤ 0.1% on the International Scale
Deep MR: MR ⁴	BCR-ABL transcript level ≤ 0.01% on the International Scale or BCR-ABL not detectable with at least 10 000 ABL or 24 000 GUS transcripts
MR ^{4.5}	BCR-ABL transcript level ≤ 0.0032% on the International Scale or BCR-ABL not detectable with at least 32 000 ABL or 77 000 GUS transcripts

CBA, chromosome banding analysis; iFISH, interphase fluorescent *in situ* hybridisation; Ph, Philadelphia; WBC, white blood cell.

Molecular monitoring

A quantification of BCR-ABL1 mRNA, performing qRT-PCR from 10 to 20 mL ethylenediaminetetraacetic acid (EDTA)-anticoagulated peripheral blood, is required every 3 months. This method represents the most sensitive tool for the assessment of the disease status, particularly of measurable residual disease. BCR-ABL1 transcript levels should be expressed according to the IS (BCR-ABL1^{IS} %) to guarantee comparability of results among laboratories. Therefore, local methods require thorough optimisation and harmonisation with reference laboratories [24–26]. Early molecular response at 3 months (BCR-ABL1^{IS} ≤ 10%) predicts survival and chance of eventually achieving DMR [27]. Intervals can be prolonged from 3 to 6 months after repeated achievement of an MMR (BCR-ABL1^{IS} ≤ 0.1%, 3 log reduction from standardised baseline) or reduced to 4–6 weeks after treatment discontinuation. Significant rises of BCR-ABL1 transcript levels (fivefold accompanied by loss of MMR) during long-term therapy are early indicators for treatment failure or non-adherence. The achievement of DMR (MR⁴, MR^{4.5}, MR⁵, i.e. 4–5 log reduction) during TKI treatment is prerequisite for therapy interruptions within controlled trials [III, A] [28].

More than 100 different kinase domain mutations of BCR-ABL1 that impair TKI binding have been reported in patients who develop TKI resistance. In the case of mutations, second-line therapy should be selected according to the sensitivity of the individual

Table 6. Definition of the response to TKI therapy (any line)

Milestones	Failure	Warning	Optimal response
Diagnosis		Score: High-risk Additional chromosomal aberrations 'major route' in Ph+ metaphases	
3 months	No CHR Ph > 95%	Ph 36%–95% BCR–ABL >10%	Ph < 35% BCR–ABL < 10%
6 months	Ph > 35% BCR–ABL > 10%	Ph 1%–65% BCR–ABL 1%–10%	Ph 0% BCR–ABL < 1%
12 months	Ph ≥ 1% BCR–ABL > 1%	BCR–ABL 0.1%–1%	BCR–ABL < 0.1%
> 18 months		BCR–ABL 0.1%–1%	BCR–ABL < 0.01%*
Anytime	Relapse, loss of MMR		

These definitions are a provisional adaptation of the original ELN definitions [6]. Operationally, 'optimal' means to continue the treatment, 'failure' to change the treatment, and 'warning' to monitor more carefully and to be ready to consider a change of treatment.

*For patients with the aim to achieve treatment-free remission.

CHR, complete haematological response; ELN, European LeukemiaNet; MMR, major molecular response; Ph, Philadelphia; TKI, tyrosine kinase inhibitor.

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mutation. In particular, *V299L*, *T315A* and *F317L/V/I/C* are resistant to dasatinib. *Y253H*, *E255K/V* and *F359V/C/I* are resistant to nilotinib, and *V299L* to bosutinib. *T315I* is resistant to all TKIs except ponatinib. Recommendations on the use of mutational analysis have recently been presented by the ELN [V, A]:

- During first-line therapy, analysis is due in the case of failure and in the case of an increase in BCR–ABL1 transcript levels leading to a loss of MMR.
- During second-line therapy, analysis is due in the case of haematological or cytogenetic failure or in the case of pre-existing mutations.
- In the case of AP or BP, mutational analysis is always due.

In any case, the mutation result should be accompanied by an estimation of the size of the mutated clone to confirm the association of refractoriness with this specific mutation [29].

Management of resistant and refractory disease

Before defining a patient as having TKI resistance and modifying therapy, treatment compliance and drug–drug interactions should be assessed.

Second and third generation TKIs

Before their approval to treat first-line CML CP, both nilotinib and dasatinib were approved for use in second-line CML CP following prior therapy including imatinib. In Europe, bosutinib is approved for CML patients previously treated with one or more TKIs and for whom imatinib, nilotinib and dasatinib are not considered appropriate treatment options.

Second-line treatment with nilotinib, dasatinib or bosutinib can yield high rates of response in patients who have inadequate response to imatinib. Dose escalation of imatinib can improve response rates in patients with inadequate response to standard-dose imatinib, but switching to second-line TKIs can be more effective. Several studies have demonstrated significantly higher rates of complete haematological response (CHR), CCyR and MMR with the newer TKIs than with high-dose imatinib. Moreover, PFS in these studies was better with the newer TKIs than with high-dose imatinib. An earlier switch to second-line TKI may be more effective than a later switch [30–32].

Bosutinib was initially studied in patients who had resistance or intolerance to imatinib. After a dose escalation period, 500 mg once daily was selected as the phase II dose. A total of 288 patients were enrolled in the pivotal phase II trial; more than two-thirds had imatinib-resistant disease. The primary endpoint of major cytogenetic response (MCyR) at 6 months was achieved in 31%; 41% achieved a CCyR. The most common toxicities were diarrhoea, nausea, vomiting and rash. Diarrhoea occurred in 84% of patients, with 9% experiencing grade 3 diarrhoea. Other notable AEs included mild myelosuppression and liver function test abnormalities [32].

Ponatinib is a third generation TKI, and the first TKI in class to exhibit activity against CML with *T315I* mutation. It is 500 times more potent than imatinib at inhibiting BCR–ABL1. After resistance or intolerance to dasatinib or nilotinib, or in the case of the *T315I* mutation, 56% of CP CML patients achieved a MCyR by 12 months on ponatinib 45 mg/day. Ponatinib should be considered the agent of choice in patients with CML and *T315I* mutation, and in instances where other TKIs are not indicated. No other commercially available TKIs have activity against this mutated BCR–ABL1. The risk of serious toxicities (vaso-occlusive disease, pancreatitis, hypertension, severe skin rashes) and of thrombotic events with ponatinib is significant, but the benefits outweigh the risks for patients with a *T315I* mutation. The incidence of these side-effects is lower with ponatinib 15–30 mg daily [33, 34].

How to select a second- or third-line option

At the time of treatment failure, patients should undergo BM examination to allow proper determination of the CML phase and documentation of any clonal evolution. All patients should have CML cells tested for *BCR–ABL1* mutational profile, as this will help guide the selection of the TKI.

For second-line treatment, the choice can be guided by the type of AEs which caused the switch, by the side-effect profiles of the different TKIs, mutational profiles, drug interactions, compliance issues and the patient's pre-existing medical conditions. Mutational analysis is required in patients who are failing imatinib or second

Table 7. Summary of recommendations

Diagnosis

- In most cases, the diagnosis can be made on the basis of a characteristic blood count and differential (excessive granulocytosis with typical left shift of granulopoiesis). Confirmation of diagnosis is obtained by the identification of the Philadelphia chromosome, 22q-, or BCR–ABL1 transcripts, or both, in peripheral blood or BM cells.
- The recognition of disease progression from CP to BP is relevant for prognosis and treatment. Immunocytology by flow cytometry and histochemistry allow accurate assessment of immature cells and distinction between myeloid and lymphoid blast crisis.
- Diagnosis must be confirmed by cytogenetics showing *t(9;22)(q34;q11)*, and by multiplex RT-PCR showing BCR–ABL1 transcripts. In rare cases, BCR–ABL1 juxtaposition can be determined by iFISH of blood cells, using dual colour dual fusion probes that allow the detection of BCR–ABL1+ nuclei. Cytogenetic assessment is required because it is necessary to detect additional chromosome abnormalities.
- Qualitative multiplex RT-PCR is carried out on blood or BM RNA. It identifies the transcript type, either typical or atypical variants. Determination of the transcript type is crucial for later monitoring, in particular for the accurate assessment of molecular response.
- Baseline mutational analysis in patients with newly diagnosed CML CP is not advised.

Staging and risk assessment

- Major route cytogenetic aberrations (+8, iso(17q), +19, +22q-), chromosome 3 aberrations and BM fibrosis at diagnosis are considered warning signs.

First-line management of chronic phase CML

- Options for first-line therapy in CML CP are imatinib 400–800 mg/day, nilotinib 300 mg twice daily or dasatinib 100 mg/day. TKI selection should be based on treatment goals, age and comorbidities and should take into consideration the AE profile of the available drugs.
- Other strategies for front-line therapy include using higher doses of imatinib or combining a TKI with an additional agent, such as IFN α .
- In individual patients, therapy goals should be discussed with the patient and defined before the selection of the first-line drug. With all three TKIs licensed for first-line therapy, survival chances are similar [I, A].
- Risk of transformation to AP and BP is lower in Sokal non-low risk patients using dasatinib or nilotinib [I, A].
- Patient's age, comorbidities and the specific TKI toxicity profile should be considered [V, B].
- For patients at risk of developing pleural effusions (existing lung disorders or uncontrolled hypertension), dasatinib should be avoided. PAH is a rare complication of dasatinib, and patients with pre-existing PAH may be considered for alternative TKIs in the front-line setting. Dasatinib also inhibits platelet function, and patients taking concomitant anticoagulants may be at an increased risk of haemorrhagic complications [V, B].
- Patients should take nilotinib on an empty stomach to avoid excess drug exposure with fat-containing food. Nilotinib has also been associated with vaso-spastic and vaso-occlusive vascular events, such as ischaemic heart disease, ischaemic cerebrovascular events and PAOD [I, C]. Nilotinib use should be prescribed with caution in patients with risk factors such as DM or coronary, cerebrovascular or peripheral arterial disease. A thorough intervention against cardiovascular risk factors such as smoking, hyperlipidaemia, hypertension and DM is warranted [V, A].
- All available TKIs may prolong the QT interval; thus, potassium and magnesium should be repleted to appropriate serum levels before starting therapy [V, B].
- TKI therapy should be commenced immediately after confirmation of BCR–ABL1 positivity. It is recommended to taper the hydroxyurea dose before its discontinuation.
- To avoid tumour lysis syndrome, 2.5–3 L fluid intake is recommended per day considering the individual cardiac and/or renal situation. Sodium bicarbonate may be used to set the urine pH to 6.4–6.8 for optimal uric acid clearance. Allopurinol may increase the risk of xanthine accumulation with renal failure and should therefore be restricted to patients with symptomatic hyperuricemia.
- If the response to TKIs is a failure, the treatment must be switched to an alternative TKI, or alloSCT should be considered. Between optimal and failure, there is a grey zone that is defined as 'warning', meaning that the response must be monitored more carefully and that the patient may be eligible for potentially better treatments [V, A].
- Cytogenetic monitoring must be carried out by analysis of marrow cell metaphases, reporting the proportion of Ph+ metaphases of at least 20 metaphases analysed. iFISH data cannot be used to calculate the cytogenetic response categories.
- A quantification of BCR–ABL1 mRNA, performing qRT-PCR from 10 to 20 mL EDTA-anticoagulated peripheral blood, is required every 3 months.
- The achievement of DMR (MR⁴, MR^{4.5}, MR⁵, i.e. 4–5 log reduction) during TKI treatment is prerequisite for therapy interruptions within controlled trials [III, A].
- During first-line therapy, mutation analysis is due in the case of failure and in the case of an increase in BCR–ABL1 transcript levels leading to a loss of MMR [V, A]. During second-line therapy, analysis is due in the case of haematological or cytogenetic failure or in the case of pre-existing mutations [V, A]. In the case of AP or BP, mutational analysis is always due [V, A].

Management of resistant and refractory disease

- At the time of treatment failure, patients should undergo BM examination to allow proper determination of the CML phase and documentation of any clonal evolution. All patients should have CML cells tested for *BCR–ABL1* mutational profile, as this will help guide the selection of the TKI.
- Mutational analysis is required in patients who are failing imatinib or second generation TKIs, or those who progress to AP/BP [V, A].
- Options are imatinib, nilotinib, dasatinib, bosutinib or ponatinib [V, A]. Ponatinib should be considered the agent of choice in patients with CML and *T315I* mutation, and in instances where other TKIs are not indicated.
- AlloSCT remains an important therapeutic option for patients in CML CP who fail at least 2 TKIs or are potentially harbouring the *T315I* mutation (after a trial of ponatinib therapy) [V, B]. Patients with a high risk for transformation should be considered for alloSCT, since outcome of alloSCT after transformation is unfavourable.
- The only curative option for patients in BP disease is alloSCT. AlloSCT should also be considered early in patients developing AP during TKI treatment or high-risk patients with insufficient treatment response [V, B].
- AlloSCT for advanced disease with a high transplant risk should not be advocated; ongoing drug treatment or best supportive care might be the better option.

Table 7. Continued

Management of AEs, quality of life

- Treatment discontinuation may be considered in individual patients, if proper, high-quality and certified monitoring can be ensured. Prerequisites for safe stopping are institutional requirements for safe supervision, identification of typical BCR–ABL1 transcripts at diagnosis, at least 5 years of TKI therapy, achievement of MR^{4.5} and a stability of DMR (at least MR⁴) for at least 2 years [III, B].

AE, adverse event; alloSCT, allogeneic stem cell transplantation; AP, accelerated phase; BM, bone marrow; BP, blast phase; CML, chronic myeloid leukaemia; CP, chronic phase; DM, diabetes mellitus; DMR, deep molecular remission; EDTA, ethylenediaminetetraacetic acid; iFISH, interphase fluorescent *in situ* hybridisation; IFN α , interferon alpha; MMR, major molecular response; MR^{4.5}, 4.5-log reduction; PAH, pulmonary arterial hypertension; PAOD, peripheral artery occlusive disease; Ph, Philadelphia; qRT-PCR, quantitative RT-PCR; RT-PCR, reverse transcriptase polymerase chain reaction; TKI, tyrosine kinase inhibitor.

generation TKIs, or those who progress to AP/BP [V, A]. Options are imatinib, nilotinib, dasatinib, bosutinib or ponatinib [V, A]. The optimisation of dosages of bosutinib (400 mg/day) and ponatinib (15–30 mg/day; 45 mg/day in advanced disease or in the case of problematic mutations) is still under investigation.

Allogeneic stem cell transplantation

The number of patients undergoing alloSCT for CML CP has decreased significantly since TKIs were introduced. AlloSCT remains an important therapeutic option for patients in CML CP who fail at least 2 TKIs or are potentially harbouring the *T315I* mutation (after a trial of ponatinib therapy) [V, B]. Patients at high risk for transformation should be considered for alloSCT, since outcome of alloSCT after transformation is unfavourable. Patients referred to transplant may have a better outcome if entering the transplant with a better response (lower CML burden). Assessment of donor availability will be prerequisite to achieve this goal.

AlloSCT in advanced stage CML

The only curative option for patients in BP disease is alloSCT. AlloSCT should also be considered early in patients developing AP during TKI treatment or high-risk patients with insufficient treatment response [V, B]. TKI monotherapy or in combination with chemotherapy may serve as a good option for those who are not candidates for transplant, or as a bridge and debulking option before alloSCT [35]. AlloSCT for advanced disease with a high transplant risk should not be advocated; ongoing drug treatment or best supportive care might be the better option and will also save costs [36].

Management of AEs, QoL

The TKIs are associated with different patterns of side-effects, and this should be considered for treatment decisions. Side-effects can be divided into three general categories. The first category includes major, grade 3 to 4 side-effects that typically occur during the initial phase of treatment, are manageable, but require temporary treatment discontinuation and dose reduction, and may lead to treatment discontinuation in ~10% of patients. The second category includes minor, grade 1/2, side-effects that start early during treatment but persist. They are also manageable and

tolerable, but affect the QoL and are a cause of decreased compliance. The third category includes late, so-called ‘off-target’ complications, which can affect the cardiovascular system, the respiratory system, liver, pancreas, the immune system, second malignancies, glucose and lipid metabolism, etc.

All TKIs can be cardiotoxic and should be used with caution in patients with heart failure. Nilotinib has been reported to be associated in particular with arterial pathology, both peripheral and coronary. Dasatinib has been reported to be associated in particular with pleura and lung complications. Because these complications are a potential cause of morbidity and mortality, continued clinical monitoring of all patients is required [37].

Treatment-free remission

TKI discontinuation studies in patients with durable DMR demonstrate that stopping TKI therapy is feasible. The Stop Imatinib (STIM) trial investigated the risk of relapse in patients on imatinib with ongoing complete molecular response for longer than 2 years who then stopped treatment. In the most recent update, 100 patients had a median follow-up of 50 months and were monitored closely for evidence of molecular relapse. Overall, 61% experienced a molecular relapse, with 95% of the events occurring within 7 months of stopping imatinib [38]. With nilotinib, at 48 weeks after stopping, 98 patients (51.6%) remained in MMR or better (primary endpoint) [39].

The economic impact of long-term discontinuation of TKI may be substantial. Ongoing studies will help to guide physicians in determining when it is safe and most promising to stop TKI therapy in CML patients.

Treatment discontinuation may be considered in individual patients, if proper, high-quality and certified monitoring can be ensured. Prerequisites for safe stopping are institutional requirements for safe supervision, identification of typical BCR–ABL1 transcripts at diagnosis, at least 5 years of TKI therapy, achievement of MR^{4.5} (4.5-log reduction) and a stability of DMR (at least MR⁴) for at least 2 years [III, B]. Less stringent criteria do not exclude successful TFR, but stability of TFR is improved with longer TKI therapy and longer DMR. Informed consent should include the information on the estimated risk of recurrence of the disease and the need for frequent molecular monitoring, monthly during the first half-year, 6-weekly during the second half-year and 3-monthly later on [40,

Table 8. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America–United States Public Health Service Grading System^a)

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, expert opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, ...), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

^aBy permission of the Infectious Diseases Society of America [43].

41]. It should be noted that a TKI withdrawal syndrome consisting of musculoskeletal pain, in most cases transient, has been observed in several cessation studies in up to 30% of the patients [42].

Methodology

These Clinical Practice Guidelines were developed in accordance with the ESMO standard operating procedures for Clinical Practice Guidelines development, <http://www.esmo.org/Guidelines/ESMO-Guidelines-Methodology>. The relevant literature has been selected by the expert authors. A summary of recommendations is shown in Table 7. Levels of evidence and grades of recommendation have been applied using the system shown in Table 8. Statements without grading were considered justified standard clinical practice by the experts and the ESMO Faculty. This manuscript has been subjected to an anonymous peer review process.

Disclosure

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