Slovenian recommendations for the management of chronic myeloid leukaemia

Irena Preložnik Zupan,[1] Karla Rener,[1] Helena Podgornik,[1] Matjaž Sever,[1] Martina Fink,[1] Mateja Grat,[2] Tadej Pajič[1]

Abstract

The paper presents recommendations for the management of patients with chronic myeloid leukaemia. Clinical manifestations, diagnostics, treatment and monitoring of treatment are presented.

Cite as: Preložnik Zupan I, Rener K, Podgornik H, Sever M, Fink M, Grat M, Pajič T. Slovenska priporočila za obravnavo kronične mieloične levkemije. Zdrav Vestn. 2018;87(3–4):191–212.

DOI: 10.6016/ZdravVestn.2713

[1] Department of Haematology, Division of Internal Medicine, University Medical Centre Ljubljana, Ljubljana, Slovenia

[2] Department of Haematology and Oncology, Non-Surgical Medical Division, General Hospital Celje, Celje, Slovenia

Correspondence:
Irena Preložnik Zupan, e: irena.zupan@kclj.si

Key words:
chronic myeloid leukemia; chronic phase; accelerated phase; blast phase; milestones of the treatment

Received: 9. 10. 2017
Accepted: 30. 1. 2018

The recommendations were adopted at the meeting of the Slovenian Haematological Society 6. 10. 2017, confirmed at the SISS on 23. 2. 2018 and the GSS SZD on 13. 3. 2018.

1 Introduction

Chronic myeloid leukaemia (CML) is a malignant disease of haematopoietic stem cells and is classified among myeloproliferative neoplasms. Its main characteristic is the presence of *BCR-ABL1* fusion gene on the altered, shortened chromosome 22, also known as the Philadelphia chromosome (Ph). Shortening of the Ph chromosome is caused by a balanced translocation between chromosomes 9 and 22 (t(9;22)(q34;q11)). CML accounts for 15–20 % of adult leukaemias and its reported annual incidence is about 1–2 new patients per 100,000 population. In recent years, the mean annual number of newly diagnosed CML patients in Slovenia was about 20. Their mean age at diagnosis was 57 years, but the disease can develop at any age, even in childhood (1-7).

The natural course of CML lasts from 3 to 5 years and the disease progresses through three different phases: the chronic phase (in which it is diagnosed in about 85 % of patients), the accelerated phase, and, eventually, the blast transformation, which is equivalent to acute leukaemia. Symptoms at the onset of CML are generally systemic (general feeling of fatigue, loss of appetite, weight loss, sweating), feeling of abdominal pressure due to the organ enlargement, less frequently bleeding due to platelet dysfunction. However, as many as 50 % of patients are asymptomatic (without problems) and the diagnosis is made based on a chance blood count. In more than half of patients the physical examination reveals marked enlargement of the spleen, less frequently enlargement of the liver. The blood count generally shows marked increase of leukocyte type cells, occasionally also of platelets (1-7).

In the past 15 years the availability of effective targeted therapies allowed patients to live their lives with almost no restrictions. In the majority of patients who show an adequate treatment response, the prognosis is excellent and their survival is equivalent or similar to that of general age-matched population. Detection and monitoring of comorbidities that may affect survival are also important. In recent years, research has focused on discontinuation of therapy and on cure of the disease. This paper presents the updated recommendations for CML diagnosis, treatment and follow-up, based on the previously published recommendations 2008 (9). In the present recommendations particular attention is also being paid to detection and management of adverse events related to tyrosine-kinase inhibitor (TKI) therapy.

2 Determination and monitoring of the disease

2.1 Confirmation of diagnosis

Patients are often referred to a haematological clinic because of incidentally discovered leucocytosis with neutrophilia and a continuous left shift (up to blasts in differential white blood cell count (DBC)), basophilia, thrombocytosis and sometimes anaemia. A detailed discussion with the patient and a careful physical examination are required, including assessment of the spleen size under the left rib margin (measured in centimetres perpendicular to the rib arch). This should be followed by a complete blood count with DBC. If the disease is found to be present, bone marrow aspiration (less frequently biopsy) is performed for morphological evaluation and genetic testing. The bone marrow cytomorphological examination shows marked bone marrow hypercellularity with granulocyte cell line overgrowth at all stages of maturation, possibly with increase in megakaryocytes and absence of fat. In over 90 % of CML patients the cytogenetic analysis shows the presence of Ph chromosome, while in the rest only the fusion gene is present, identified by fluorescence *in situ* hybridisation (FISH). Cytogenetic analysis is essential for detection of possible additional chromosomal changes (7,10,11). At the molecular level, the presence of *BCR-ABL1* fusion gene is confirmed by a typical mRNA transcript detected by the reverse transcriptase polymerase chain reaction (RT-PCR) in a peripheral blood or bone marrow sample. Depending on the location of the two breakpoints on the chromosomes 9 and 22, translocation can yield different variants of the *BCR-ABL1* fusion gene, leading to formation of various mRNA transcripts (e13a2, e14a2, less frequently e1a2, e19a2 …) and BCR-ABL1 proteins of different lengths (p210, p190, p230). At the time of the diagnosis, type of the BCR-ABL1 transcript should always be determined and documented in the patient's medical record, as it is required for treatment follow-up (12,13). At the diagnosis, the BCR-ABL1 transcript type (e13a2, e14a2) in venous blood is routinely determined and expressed on the international scale (IS).

When the disease is confirmed, routine blood chemistry is performed as well, including magnesium levels, liver (ALT, AST, gamma GT, bilirubin), renal (urea, creatinine) and pancreatic (amylase, lipase) function tests, and blood cholesterol levels. Due to the possible adverse events of the targeted treatment, the risk of cardiovascular complications and the risk of exacerbation of other chronic diseases should also be determined at the time of diagnosis. ECG

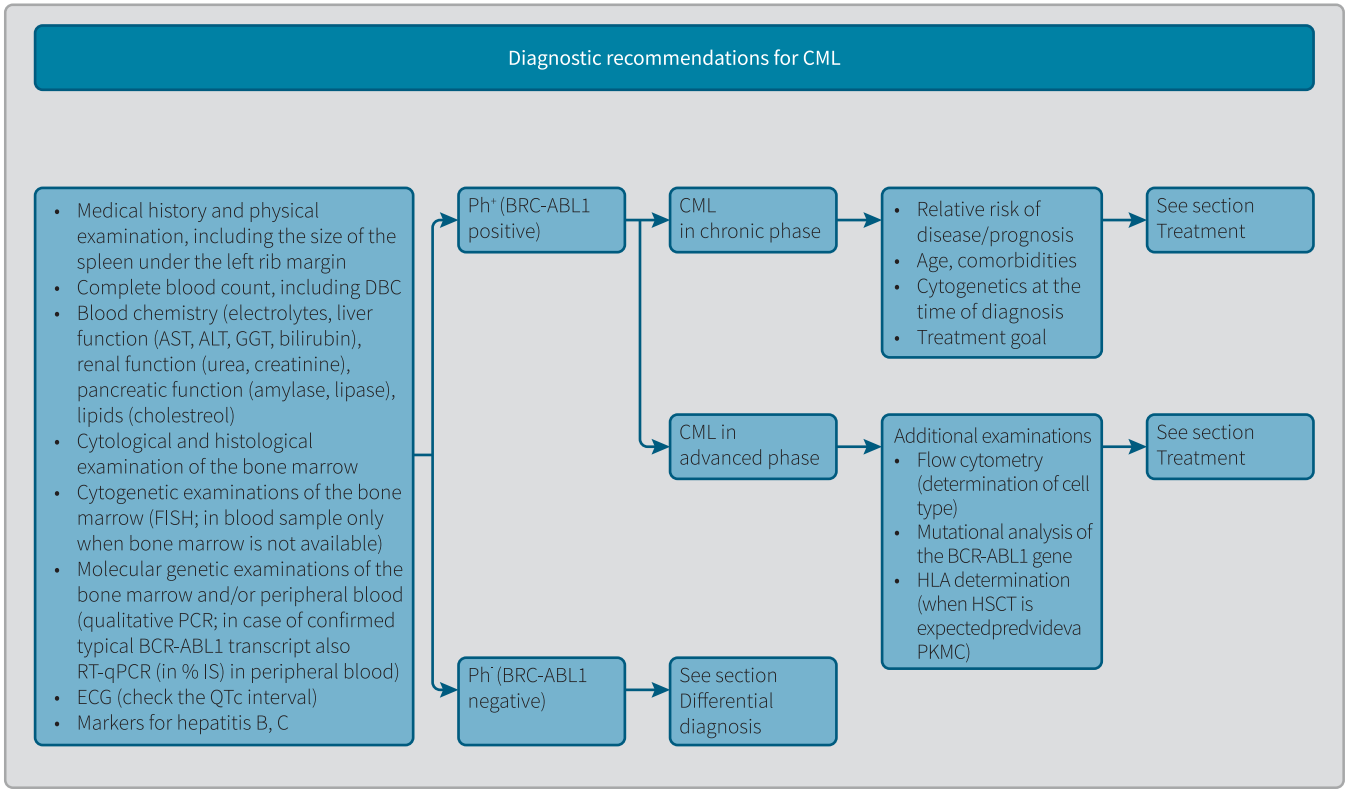

Figure 1: Diagnostic recommendations for CML

DBC – differential blood count, AST – aspartate aminotransferase, ALT – alanine aminotransferase, GGT – gamma GT, HSCT – haematopoietic stem cell transplantation, HLA – human leukocytic antigens.

should always be recorded before treatment (QTc interval), and echocardiography should be performed, if necessary. Hepatitis markers should be evaluated because of the risk of hepatitis reactivation (7,10,11,14,15). Diagnostic recommendations are presented in Figure 1 (V, A).

2.2 Differential diagnosis

Chronic myelomonocytic leukaemia (CMMoL) is a *BCR-ABL1*-negative myelodysplastic/ myeloproliferative neoplasm (MDS/MPN), which differs from CML by the presence of dysplastic changes, more pronounced cytopenia, monocytosis, and lack of basophilia. Two criteria must be met for the diagnosis of CMMoL: monocytosis $\geq 1 \times 10^9$/L, and monocyte proportion ≥ 10 % of the total leukocyte number in the differential leukocyte blood count. The most commonly mutated genes in CMMoL are *SRSF2*, *TET2* and/or *ASXL1*, found in more than 80 % of patients with CMMoL (16).

Chronic neutrophilic leukaemia (CNL). CML with BCR-ABL1 p230 protein is very similar to chronic neutrophilic leukaemia because of predominant neutrophilia. Presence of the *BCR-ABL1* fusion gene or the Ph chromosome resolves the diagnostic dilemma. Important criteria for diagnosis of CNL are: the number of blood leukocytes $\geq 25 \times 10^9$/L, segmented and band neutrophil granulocytes ≥ 80 %, promyelocytes, myelocytes and metamyelocytes

less than 10 %, rare myeloblasts, monocytes < 1×10^9/L, no dysgranulopoiesis; hypercellular bone marrow with an increased proportion and number of neutrophil granulocytes with normal maturation, and less than 5 % of myeloblasts; WHO criteria for CML, polycythaemia vera, essential thrombocythaemia, or primary myelofibrosis are not met. In presence of eosinophilia rearrangements of the *PDGFRA*, *PDGFRB*, *FGFR1* and *FGF1* genes as well as *PCM1-JAK2* fusion gene (16) should be excluded.

Atypical CML, BCR-ABL1 negative is a rare form of MDS/MPN. *SETBP1* and/or *ETNK1* gene mutations can be detected in one third of patients. Atypical CML is not associated with *JAK2*, *CALR* and *MPL* gene mutations that are in large proportion present in some MPNs.

Essential thrombocythaemia (ET). In rare cases of CML, thrombocytosis without leukocytosis may be found. Basophilia is often present as a diagnostic tip. These patients are identified by cytogenetic and/or molecular diagnostics confirming/excluding presence of Ph chromosome and the *BCR-ABL1* fusion gene (16).

Primary myelofibrosis (PM). In PM – like in CML – leukocytosis with left shift in differential leukocyte blood count is present. Cytogenetic and/or molecular diagnostics are decisive, confirming or excluding Ph chromosome and the *BCR-ABL1* fusion gene (16).

2.3 Determination of the disease phase

At the time of diagnosis, the disease phase (chronic, accelerated, blast transformation) is invariably determined based on physical examination, blood count, bone marrow cytology, and cytogenetics. (Table 1). The new 2016 revised WHO classification of myeloid neoplasms also includes the genetic evolution and resistance to tyrosine-kinase therapy into the assessment of the accelerated phase of CML (16). The European LeukemiaNet (ELN) criteria for phase determination did not change (15). Today, most patients are diagnosed in the chronic phase. This includes all patients who do not meet the criteria for accelerated phase or blast transformation. During the period 2007–2012, 544 new CML patients were registered in the Swedish CML registry: 508 (93.4 %) patients in the chronic phase and 36 (6.6 %) patients in the advanced phase (20 in accelerated period and 16 in blast transformation) (18). In Slovenia, 223 patients with CML were diagnosed during the period 2002–2014: 212 (95 %) patients in the chronic phase and 11 (5 %) patients in the advanced phase (9 (4 %) in accelerated phase and 2 (1 %) in blast transformation) (personal data).

2.4 Disease prognosis

The prognostic factors can be divided into two groups: (1) factors present at the time of diagnosis and (2) treatment response related factors.

Important prognostic factors at the time of the diagnosis are:

- **CML phase** – the accelerated phase and the blast transformation phase are prognostically unfavourable. Patients diagnosed and starting treatment in the chronic phase have a significantly better survival compared to patients diagnosed and initiating treatment in the advanced phase of the disease.
- **Additional clonal chromosomal abnormalities in Ph^+ cells (ACCA/Ph^+),** in particular the major route aberrations (+8, +Ph, i(17)(q10), ider(22)(q10)t(9;22), +19) may be prognostically disadvantageous and associated

with shorter survival and faster disease progression.

- **The relative risk of disease** based on pre-treatment clinical and laboratory data, assessed by Sokal, Hasford and/or EUTOS prognostic scores (Table 2) (19-21). The Sokal and Hasford scores classify the relative risk of decreased survival duration into low, intermediate and high, while the EUTOS score divides it into low and high. Since 2016, the ELTS (EUTOS long-term survival score) is also available. The ELTS score takes into account age (in years), spleen size, percentage of blasts in the blood, and platelet number. All these scores can be determined at the website www.

Table 1: Definitions of accelerated phase and blast transformation in CML; reproduced from the European Leukemia Net (ELN) recommendations and the new revision of the WHO classification 2016 (15,16).

	Definition
Accelerated phase	
ELN criteria	• 15–29 % of blasts in blood and/or BM
	• > 30 % blasts + promyelocytes in blood or BM, with < 30 % blasts
	• > 20 % of basophils in blood
	• Persistent thrombocytopenia < 100×10^9/L (not after therapy)
	• Additional treatment-emergent clonal chromosomal abnormalities in Ph^+ cells (ACCA/Ph^+)
WHO criteria* (one or more of the listed criteria, although one is sufficient)	• Leukocyte count ≥ 10×10^9/L or increasing in spite of therapy
	• Splenomegaly, or increasing splenomegaly in spite of therapy
	• Persistent thrombocytosis (> $1{,}000 \times 10^9$/L) in spite of therapy
	• Persistent thrombocytopenia (< 100×10^9/L) unrelated to therapy
	• ≥ 20 % basophils in blood
	• 10–19 % of blasts in blood and/or BM
	• ACCA/Ph^+ at the initial diagnosis, containing »major route« aberrations
	• Any treatment-emergent ACCA/Ph^+
Blast transformation	
ELN criteria	• ≥ 30 % of blasts in blood or BM
	• Extramedullary leukaemic blast cell proliferation
WHO criteria	• ≥ 20 % blasts in blood and/or BM**
	• Extramedullary blast cell accumulation

Blasts – leukaemic blast cells, BM – bone marrow, basophils – basophil granulocytes, ACCA/Ph^+ – additional clonal chromosomal abnormalities in Ph^+ cells; * New, revised WHO classification 2016; ** As lymphoblastic transformation may be very abrupt, even the appearance of small number of lymphoblasts represents an immediate alarm, requiring further diagnostics and initiation of treatment.

leukemia-net.org/content/leukemias/cml/. Prognostic scores were developed at different time periods, when need for evaluation of therapeutic effect of new medicines emerged. Thus, the Sokal score was introduced in 1984 for monitoring effectiveness of hydroxyurea therapy, the Hasford score in 1998 for monitoring effectiveness of interferon therapy, and the EUTOS score in 2011 for monitoring effectiveness of tyrosine-kinase inhibitors therapy. Currently, all three are still in use.

During the treatment it is prognostically important:

- **Whether desired treatment milestones are achieved in appropriate treatment period.** Parameters of interest are haematological, cytogenetic and molecular responses as well as the depth of response (see section Monitoring the treatment success). Two key factors related to long survival are: (1) early molecular response; BCR-ABL1 transcript after 3 to 6 months of treatment ≤ 10 % on the international scale (IS) (BCR-ABL1^{IS}) (2), major molecular response; BCR-ABL1^{IS} transcript after 12 months of treatment ≤ 0.1 %,
- **Clonal evolution** at any time during treatment. ACCAs/Ph^{+} indicate disease progression. They may already be present at the time of diagnosis, but generally develop as the disease progresses; that is why this is called clonal evolution. Additional clonal chromosomal abnormalities are present in about 80 % of patients in blast transformation. The most common are the so-called major route aberrations of clonal evolution that carry a greater risk for CML patients (23). ACCA/Ph- cells are currently not considered to belong to the unfavourable prognostic group, with the exception of patients with chromosome 7 abnormalities (monosomy, deletion) that may be associated with an increased risk of myelodysplastic syndrome or acute leukaemia (15),

Table 2: Assessment of relative risk of disease by Sokal, Hasford and EUTOS scores (19-21).

	Sokal score	Hasford score	EUTOS score
Age (years)	0.116 × (age - 43.4)	0.666 when age < 50 years	/
Spleen (cm below the LCM)	0.0345 × (spleen - 7.51)	0.042 × spleen	Spleen × 4
Platelets, × 10^9/L	0.188 × [(plt ÷ 700)^2 - 0.563]	1.0956 when plt ≥ 1500 × 10^9/L	/
Myeloblasts (blood), %	0.0887 × (myeloblasts - 2.10)	0.0584 × myeloblasts	/
Basophil granulocytes, %	/	0.20399 when baso > 3 %	Basophils × 7
Eosinophilic granulocytes, %	/	0.0413 x eosino	/
Relative risk			
Low	< 0.8	≤ 780	≤ 87
Intermediate	0.8–1.2	781–1480	/
High	> 1.2	>1480	> 87

- **Unexpected increase in the BCR-ABL1 transcript**, which is regularly monitored with RT-qPCR. This is an important dynamic factor in deciding on further treatment choices. It is associated with the presence of the *BCR-ABL1* gene kinase domain mutations, loss of treatment response or patient treatment compliance.

2.5 Monitoring treatment success

Regular clinical and laboratory monitoring is crucial for assessing the treatment response, as well as for an early detection of potential irregular medication use (non-adherence), resistance to treatment, or treatment failure. Treatment success is evaluated based on haematological, cytogenetic and molecular responses in a given time period (15,24) (Table 3). Complete haematological response means complete normalisation of the blood count and nonpalpable spleen on physical examination. The degree of cytogenetic response is determined based on the proportion of Ph^+ metaphases. Molecular response is determined considering the BCR-ABL1 transcript levels on the IS, assessed by RTqPCR.

Treatment success can be monitored using cytogenetic and molecular genetic techniques. As the vast majority of TKI-treated CML patients achieve

Table 3: Definitions of haematological, cytogenetic, and molecular response and relapse (15,24).

Definition	
Haematological response (complete) – CHR	• Platelets < 450×10^9/L • Leukocytes < 10×10^9/L • DBC – no immature cells and < 5 % basophils • Non-palpable spleen, no signs and/or symptoms of disease
Cytogenetic response (CyR)	• Complete (CCyR): no Ph^+ metaphases – 0 % • Partial (PCyR): Ph^+ metaphases – 1 to 35 % • Major (MCyR): Ph^+ metaphases – 0 to 35 % (CCyR + PCyR) • Minor (MinCyR): Ph^+ metaphases – > 35 %
Molecular response (MolR)	• Early (EMolR) – BCR-ABL1 ≤ 10 % (IS) at 3 and 6 months • Major (MMolR) – BCR-ABL1 ≤ 0.1 % (IS) • Deep MolR (DMolR): Molecular response 4.0 (Mol 4.0): • The disease is detectable (positive) ≤ 0.01 % $BCR\text{-}ABL1^{IS}$ and > 0.0032 % $BCR\text{-}ABL1^{IS}$ or • The disease is not detectable with a threshold sensitivity RTqPCR 4-log* Molecular response 4.5 (Mol 4.5): • The disease is detectable (positive) ≤ 0.0032 % $BCR\text{-}ABL1^{IS}$ and > 0.001 % $BCR\text{-}ABL1^{IS}$ or • The disease is not detectable with a threshold sensitivity RT-qPCR 4.5-log* Molecular response 5.0: • The disease is detectable (positive) ≤ 0.001 % $BCR\text{-}ABL1^{IS}$ or • The disease is not detectable with a threshold sensitivity RT-qPCR 5-log*
Relapse/recurrence	• Loss of response (defined as haematological or cytogenetic relapse) • 5-fold increase in $BCR\text{-}ABL1^{IS}$ transcript levels with loss of MMolR – imperative bone marrow sample for cytogenetic examination (possible loss of PCyR) and for BCR-ABL1 mutation analysis; is not itself defined as relapse

BCR_ABL1^{IS} – Level of expression of *BCR-ABL1* gene (on International scale (IS)) in WBCs from peripheral blood; DBC – Differential white blood cell count; *Sensitivity limit of RT-qPCR is defined according to the reference gene copies number (ABL1 or beta-glucoronidase (GUSB)) in the sample of complementary DNA (cDNA), in accordance with reference 24.

a complete cytogenetic response within a year of treatment initiation (25,26), and as regular cytogenetic bone marrow sample examinations represent a much higher patient burden vs. the BCR-ABL1 transcript level assessment in venous blood, regular RT-qPCR monitoring is deemed completely adequate considering the high quality of BCR-ABL1 transcript level assessment in Slovenia (international control, results expressed on international scale, issued within 14 days). Transcript levels are determined every 3 months until the confirmed major molecular response and every 3–6 months thereafter (Table 4 and Table 5). Cytogenetic examination and mutational analysis of the *BCR-ABL1* fusion gene should be performed in case of treatment milestones not being achieved as well as in case of loss of treatment response or BCR-ABL1 transcript levels increase (more than 5-fold) and loss of major molecular response on two suc-

Table 4: Treatment milestones in CML patients (any time) receiving TKI (10,5,17)

Time	Adequate Response	Warnings	Failure
At diagnosis	/	High relative risk or ACCA/Ph^+, major routes*	/
At 3 months	BCR-ABL1 < 10 % or Ph^+ ≤35 %	BCR-ABL1 > 10 % or Ph^+ 36–95 %	No CHR or Ph^+ > 95 %
At 6 months	BCR-ABL1 < 1 % or Ph^+ 0 % (CCyR)	BCR-ABL1 1–10 % or Ph^+ 1–65 % (PCyR)	BCR-ABL1 > 10 % or Ph^+ >35 %
At 12 months	BCR-ABL1 < 0.1 % (MMolR)	BCR-ABL1 0.1–1 %	BCR-ABL1 >1 % or Ph^+ ≥ 1 %
> 18 months	BCR-ABL1 < 0.01 %	BCR-ABL1 0.1–1 %	ACCA/Ph^+ Confirmed MMolR loss § Mutations

*High relative risk of disease (Sokal or Hasford or EUTOS) and/or additional clonal chromosomal abnormalities in Ph^+ cells (ACCA/Ph^+), major route aberrations: +8, +Ph, i(17)(q10), ider(22)(q10)t(9;22), +19; § Confirmed by two successive assessments, where the second value is ≥ 1 % IS, except when associated with loss of complete haematological response or complete cytogenetic response.

Adequate response	• Further monitoring of milestones according to the protocol • Monitoring for treatment-related adverse events	• Continuation of the same TKI
Warnings	• Check whether patient is receiving the medicine regularly • Interactions with other medicinal products • Mutational analysis • Cytogenetic analysis	• Switch to another TKI or continuation of the same TKI • Increase of TKI dose • Assessment of need for alloHSCT
Failure	• Check whether patient is receiving the medicine regularly • Interactions with other medicinal products • Mutational analysis • Cytogenetic analysis	• Switch to another TKI and • Assessment of need for alloHSCT, initiating the procedure

TKI – tyrosine kinase inhibitor; alloHSCT – allogeneic haematopoietic cell transplantation

cessive assessments in up to 3 months intervals (15). Mutational analysis of the *BCR-ABL1* gene using the classic Sanger sequencing technique plays an essential role in detection of changes in the fusion gene that cause TKI therapy resistance (15,27), while the cytogenetic examination provides possibility of the major route ACCAs detection that imply accelerated course of the disease (28). It is reasonable to repeat cytogenetic examination even in patients showing adequate treatment response at least after a year of TKI therapy and whenever unexpected blood count changes suggesting myelodysplasia occur. During the TKI therapy another cytogenetic feature is encountered, namely finding of cytogenetic changes in Ph-negative metaphases (ACCA/Ph-); these are observed in about 10 % of treated patients. Significance of the majority of these changes (the most common among them being chromosome 8 trisomy) is not known. However, some of them – in particular chromosome 7 abnormalities – are associated with a higher risk of MDS. All of the abovementioned cytogenetic and molecular genetic examinations are regularly performed in the Specialized Laboratory of the Clinical Department of Haematology at the UCC Ljubljana. The latter is the only Slovenian institution certified by the European Leukemia Network (ELN) for reporting molecular response on the International Scale (IS).

3 Treatment

The following therapeutic options are available for the treatment of CML (8):

1. Control of disease with tyrosine-kinase inhibitors (as yet there is no ev-

Table 5: Overview of treatment success monitoring with genetic testing

Test	Recommendation
Cytogenetics (bone marrow)	• At the diagnosis and then • Every 6 months until the complete cytogenetic response is confirmed any time • When the major molecular response is lost • When blood count changes suggest myelodysplasia
Qualitative PCR (bone marrow or peripheral blood)	• At the diagnosis – determination of the BCRABL1 transcript type
Quantitative RT-PCR (RT-qPCR) (blood)	• At the diagnosis then • Every 3 months until the major molecular response (MMolR) is confirmed thereafter • Every 3 to 6 months
BCR-ABL1 kinase domain mutational analysis (blood)	In case of: • Unsatisfactory response at the desired time • Loss of response • Disease progression

RT-qPCR, reverse transcription (RT) and quantitative real time polymerase chain reaction (qPCR).

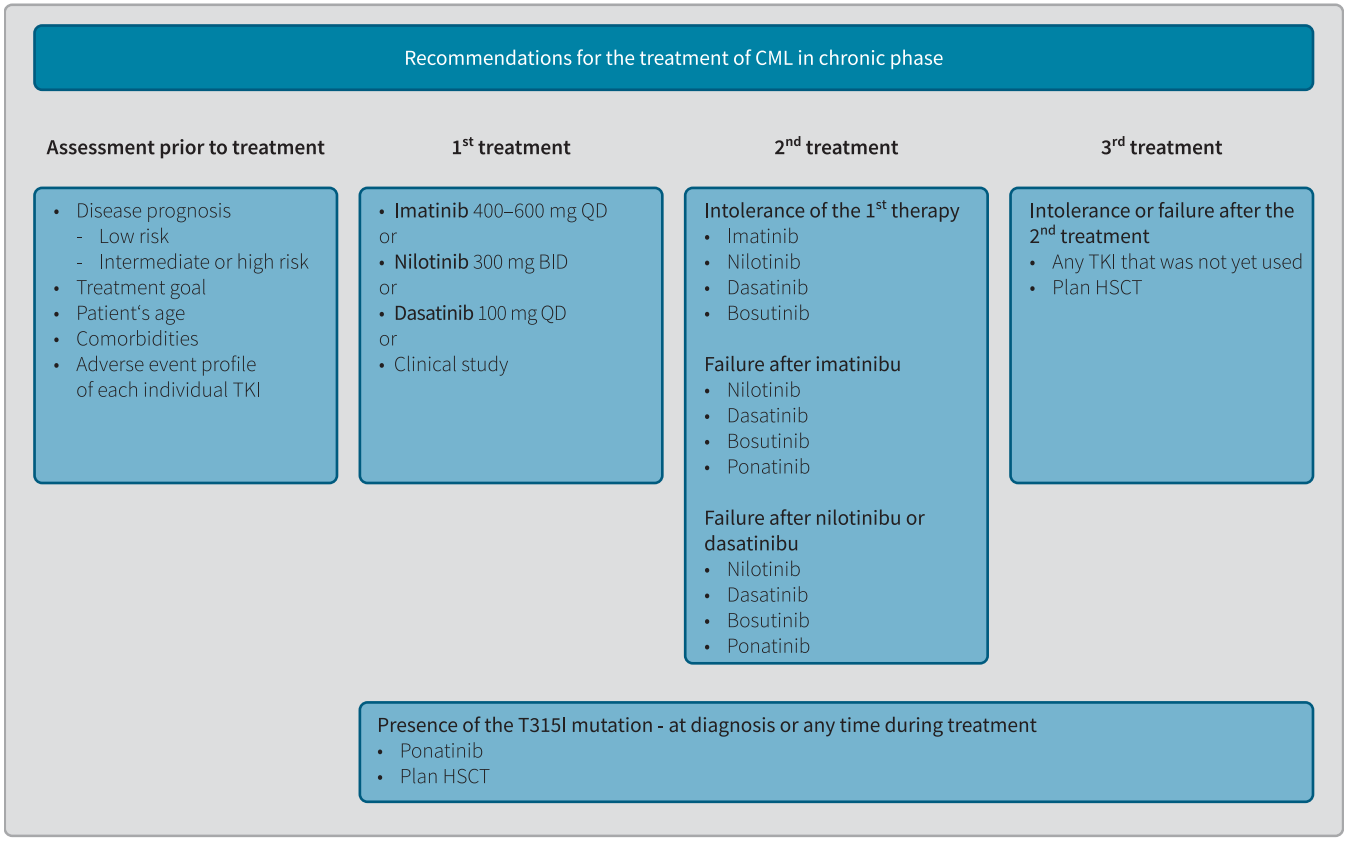

Figure 2: Recommendations for the treatment of CML in chronic phase
HSCT – haematopoietic stem cell transplantation. For detailed explanation see section Treatment.

idence yet that this type of treatment is curative).
2. Allogeneic haematopoietic stem cell transplantation (alloHSCT) that is potentially curative.
3. Palliative cytostatic treatment.

TKIs are as yet the most effective pharmacotherapy and have changed the prognosis of CML patients. A prerequisite for success is appropriate therapy and monitoring of patients according to the current management guidelines (8,10,15,17). TKIs are in clinical use since 2001, when the first generation TKI imatinib was approved by FDA. The following factors should be considered when selecting therapy: disease phase and cytogenetics, chronic comorbidities, patient age, adverse event profile of the drugs, availability of a BSC donor, response to TKI therapy and, of course, patient's abilities and preferences. AlloHSCT is not among the methods for the initial treatment of CML in its chronic phase any longer; it is now selected only in rare patients diagnosed during the blast transformation, in patients with T315I mutation and other mutations in the *BCR-ABL1* that herald resistance to TKI therapy, in rare patients who do not tolerate/are intolerant to treatment with multiple TKIs, and in patients in who the disease progresses in spite of treatment with multiple TKIs.

3.1 Treatment of the chronic phase of CML

Initial treatment of patients in the chronic CML phase includes the first generation (imatinib 400–800 mg / day) and the second generation TKIs (dasatinib 100 mg/day and nilotinib 300 mg 2 ×/day) (8,10,15,17); these medicines were approved based on the registration studies IRIS, DASISION and ENESTnd (29-31). The survival probabilities are the same for all three medicines (17). Hydroxyurea (40 mg/kg body weight) can be given initially, prior to confirmation of BCR-ABL1 positivity, to achieve cytoreduction in patients with high leukocytosis. A TKI should be initiated immediately after confirmation of BCR-ABL1 positivity. Hydroxyurea should be discontinued by tapering the dose. Intake of 2–3 litres of fluid daily is recommended in order to avoid tumour lysis syndrome. Beside the definition of the treatment goal, selection of the most appropriate TKI for the first therapy should also consider the following diagnostic findings (which should always be documented in patient's medical records before the treatment initiation) (see Figure 2):

- The relative risk of the disease prior to treatment (by Sokal, Hasford and/or EUTOS scores, and ELTS).
- Patient's age and comorbidities: Nilotinib should be avoided in patients with high risk of cardiovascular complications and dasatinib in patients with pulmonary diseases or previous pleural effusions. Comorbidities are the main cause of mortality among patients with CML during TKI treatment (22,32). The website www.hematologija.org provides a questionnaire and a handy table for the assessment of cardiovascular risk, both based on the European guidelines for cardiology.
- Cytogenetics at the time of the diagnosis: ACCA/Ph$^+$, in particular the major route aberrations (+8, +Ph, i(17)(q10), ider(22)(q10)t(9;22), +19) that are associated with a worse prognosis.

Recommendation 1 **I A**

Prior to the decision on the first therapy, the desired treatment goals should be considered in each individual patient.
The survival probabilities are equivalent with all three TKIs that are currently available for the initial treatment of CML. 5-year survival rate is 85–95 %.

Patients with a low relative risk at the time of diagnosis may receive imatinib, dasatinib or nilotinib at the standard dose. From the financial standpoint, imatinib is more acceptable than other TKIs. However, patients with intermediate or high risk as well as patients requiring rapid and deepest possible response (e.g. patients with expected longer survival; patients wishing to gradually discontinue the treatment; women wishing to get pregnant etc.) are likely to achieve greater therapeutic benefit from the second generation TKIs (10,15). Dasatinib is the medicine of choice in patients with previous cardiovascular diseases, pancreatitis or hyperglycaemia, and nilotinib in patients with previous pulmonary diseases or risk of pleural effusions (10). Prognosis and survival are significantly worse for patients with ACCA/Ph$^+$. Evidence shows that there are about 2–4 % of such patients. The treatment decision should be individualised (23,33).

Recommendation 2 **I A**

Dasatinib- or nilotinib-treated patients with intermediate or high risk of disease have lower danger of transition into the accelerated phase and blast transformation.

According to the currently available data, generic imatinib is safe and effective (34). As the patient's adherence plays a crucial role in achieving the desired treatment results, patient's abilities, problems and wishes also have to be considered when deciding on either treatment choice or treatment change. For this purpose the website www.hematologija.org provides a short questionnaire that patients can complete at each visit at the haematology clinic.

Recommendation 3 **V B**

Patient's age, comorbidities and adverse events profile of the individual medicine should all be considered prior to initiation of the treatment.

Resistance to TKI therapy is either primary – patients do not achieve the desired treatment milestones in spite of regular use of medicines – or secondary – patients lose the treatment success after having initially achieved appropriate responses to TKI therapy. The most common causes of the primary resistance are the aberrant expression of TKI transporters and binding of TKI to plasma proteins. Measurements of imatinib plasma levels are not established in routine clinical practice; however, they are undoubtedly useful for assessment of treatment adherence. In Slovenia, a method for determination of plasma and intracellular concentrations of TKIs was established in collaboration with the Faculty of pharmacy (35). The most common causes of the secondary resistance to TKI therapy are point mutations in the *BCR-ABL1* fusion gene (Table 6); therefore, in such case a mutational analysis is required and its results provide the basis for treatment modification and choice of further treatment (10,15,17).

Early molecular response at 3–6 months of TKI therapy (≤ 10 BCR-ABL1^{IS}) has an important prognostic significance for long-term progression-free survival. When this treatment milestone is not achieved, it is always necessary: (1) to check whether the patient is using his/her medicines regularly and (2) to perform mutational analysis of the *BCR-ABL1* fusion gene. Receiving less than 90 % of the medication per month is associated with a worse treatment response (36). Mutational analysis of the *BCR-ABL1* fusion gene allows appropriate drug selection (15,17,37) (Table 6).

3.2 Treatment of the advanced disease phase (at the time of diagnosis and later during TKI treatment)

In the advanced phase of disease, therapy selection is based on patient's age and comorbidities. Prognosis tends to be worse in patients experiencing disease progression during the TKI therapy; in this group the TKI choice depends on the previous treatment. Mutational analysis is recommended in all patients with advanced phase of the disease (17). TKI is selected based on the previous treatment and the results of the mutational analysis (15,17,37) (Table 6 and Figure 2). A large proportion of patients achieve major cytogenetic response without simultaneous haematological response (due to persistent cytopenia);

this is associated with a worse treatment outcome.

The following TKIs are available for the treatment of advanced CML: the first generation TKI imatinib (2 × 400 mg/day), the second generation TKIs dasatinib (2 × 70 mg/day or 1 × 140 mg/day), nilotinib (2 × 400 mg/day – in the accelerated phase) and bosutinib (500 mg/day), and the third generation TKI ponatinib (45 mg/day). Omacetaxine is not licensed in Slovenia. Nilotinib is not indicated in the CML blast transformation phase (8,10,15,17).

Recommendation 4 **V A**

In case of advanced disease treatment with appropriate doses of imatinib, nilotinib, dasatinib, bosutinib or ponatinib should be considered. The choice of the therapy depends on previous treatment and mutational analysis. Ponatinib is used in patients with T315I mutation.

In the accelerated CML phase TKI therapy is recommended for newly diagnosed patients. Most patients respond well to the treatment. Decision for alloHSCT is based on response to TKI therapy and should in general be considered only in patients not achieving optimal responses to the therapy. In patients progressing to accelerated CML phase during the TKI therapy, switch to another TKI is recommended as bridging to alloHSCT, when the latter is appropriate for the patient.

Blast transformation of CML. The alloHSCT is considered as the first-line therapy in only very few patients; in others, combination of TKI and chemotherapy is used, as for acute lymphoblastic or myeloblastic leukaemia. Lumbar puncture and prophylaxis of the central nervous system (CNS) disease is recommended in lymphoblastic transformation. Dasatinib passes the blood-brain barrier and is the most appropriate therapy for patients with CNS involvement (10).

The review of data of the newly diagnosed CML patients during the 5-year period 2007–2017 (18) showed that among 437 such patients, diagnosed in the chronic phase of CML, progression of the disease was observed in 18 patients: in 5 patients it progressed into the accelerated phase and in 13 into the blast transformation. Based on morphological characteristics, blast transformation was lymphoblastic in 6 patients, myeloblastic in 6 patients, biphenotypic in 1 patient.

Table 6: Selection of TKI therapy based on the mutational analysis (10,15,17,37).

BCR-ABL1 point mutations	Recommended TKI selection
Y253H, E255K/V, F359V/C/I	Dasatinib
F317L/V/I/C, T315A, V299L	Nilotinib
E255K/V, F317L/V/I/C, F359V/C/I, T315A, Y253H	Bosutinib
T315I	Ponatinib, omacetaxine, alloHSCT
Other	Based on *in vitro* susceptibility of the cell clone with mutation for TKI, or based on clinical experience

TKI – tyrosine kinase inhibitor; alloHSCT – allogeneic haematopoietic cell transplantation.

The probability of disease progression was 3.1 % in the first year and 4.3 % in two years. 24 patients (5.4 %) died within two years of diagnosis, without CML transformation into the advanced phase. In 3 patients death was CML-related, in others it was not. None of these patients was appropriate candidate for alloHSCT. In the same period, 36 patients were newly diagnosed in the advanced CML phase (20 patients in the accelerated phase, 16 in blast transformation [8 in lymphoblastic and 8 in myeloblastic]). Most of these patients – including 18 patients progressing within 24 months after the diagnosis – were treated with imatinib. In Sweden, nilotinib as the first-line treatment only became available in December 2011. Rigorous following of the guidelines is extremely important for achieving good treatment results.

3.3 Haematopoietic cell transplantation in CML patients

With the introduction of imatinib into the CML treatment, the number of HSCT decreased dramatically all over the world. The role of alloHSCT depends on the treatment result achieved with TKI. HSCT is only performed in specific groups of CML patients (10,15,38): (1) In patients diagnosed in accelerated phase/blastic transformation, alloHSCT provides the possibility of long-term survival to about half of patients with progressive disease and about 10–20 % of patients with blast transformation; (2) Patients with TKI treatment failure: prior to being candidates for HSCT, all patients should get therapy with a second generation TKI in attempt to achieve the second chronic CML phase; (3) Patients with mutations resistant to TKI therapy: the most common is the T315I mutation that causes resistance to all first and second generation TKIs. In this group too, HSCT is more successful if performed after the best possible treatment response to ponatinib.

Prior to transplantation, the probability of HSCT success in CML can be estimated using the modified prognostic system. Factors influencing the success of HSCT include type and matching of donor and recipient, CML status, patient age, donor-recipient gender matching, and time from the diagnosis to HSCT. Survival rates range from about 75 % in the prognostically most favourable group to about 19 % in the unfavourable group. Related matching donor is preferred, when available. Most patients receive haematopoietic stem cells obtained from venous blood. Myeloablative combination with busulfan and cyclophosphamide is the most frequently used conditioning regimen. Nonmyeloablative conditioning is used in elderly patients and patients with comorbidities. Following HSCT, BCR-ABL1 transcript is monitored by RQ-PCR for the detection of possible recurrence of the disease. TKIs or infusion of donor lymphocytes are used for prophylaxis of recurrence and treatment of haematological relapse. Annually, approximately one CML patient in Slovenia receives transplantation during the TKI treatment of CML. Autologous HSCT is no longer used in the treatment of CML.

3.4 Treatment milestones

Regular clinical and laboratory monitoring of patients according to the guidelines plays an essential role in pro-

viding success and long-term survival (18). Treatment response evaluation is performed at specified time intervals, as are monitoring for possible irregular drug use (non-adherence), treatment resistance and treatment failure (Table 4).

Recommendation 5 **V A**

Mutational analysis should be performed:
- during the 1st and the 2nd treatment – in case of an unsatisfactory response within the desired time, and in case of loss of response
- in advanced disease – whenever it develops;

3.5 Discontinuation of TKI therapy

Based on previous clinical experience, TKI therapy discontinuation is possible and safe in a specific subgroup of patients; after the discontinuation, these patients have to be monitored even more carefully than during the treatment. Discontinuation is only possible in agreement with the patient, who needs to be aware of the risks and benefits of treatment discontinuation. According to the past experience, some patients report marked withdrawal symptoms after TKI discontinuation; therefore, patients should be informed of such possible problems prior to discontinuation (10,17,33). Currently, study results show the probability of relapse-free and therapy-free survival to be about 40–60 %. The longest follow-up is 5 years. Most recurrent cases develop within 6 months of TKI discontinuation (10). Nilotinib is the only TKI for which the possibility of controlled treatment discontinuation is stated in its Summary of product characteristics (SmPC) (39).

Criteria for treatment discontinuation according to the National Comprehensive Cancer Network (NCCN) guidelines (10) are:

- Age ≥ 18 years.
- CML in chronic phase; patient never exhibited signs of advanced or TKI-resistant disease.
- At least 3 years of TKI therapy.
- Stable deep molecular response (MolR); ≥ 4-log reduction of BCR-ABL1 transcription (MolR 4; ≤0.01 % BCR-ABL1^{IS}) for at least 2 years.
- Access to appropriate molecular laboratory that ensures sensitivity for

Table 7: Haematological adverse events of TKI and their management.

Haematological adverse events	Management
Haematological • Neutropenia (Grade 3–4); NG < 1×10^9/L • Thrombocytopenia (Grade 3–4); Plt < 50×10^9/L • Anaemia (Grade 3–4); Hb < 80 g/L	Dose reduction of imatinib to 300 mg/day, nilotinib to 400 mg/1 ×/day, dasatinib to 50–70 mg/1 ×/day, bosutinib to 100 mg/day, ponatinib 15–30 mg/day or discontinuation in case of NG < 1×10^9/L or Plt < 50×10^9/L; administration of growth factors, such as GCSF, in case of resistant neutropenia. Transfusion in symptomatic anaemia. Rule out iron deficiency, vitamin B12 deficiency and folic acid deficiency.

NG – neutrophil granulocytes, Plt – platelets, Hb – haemoglobin concentration, G-CSF – Granulocyte colony-stimulating factor.

Table 8: Nonhaematological TKI adverse events and their management.

Nonhaematological adverse events	Management
Imatinib	
• Diarrhoea	• Supportive measures
• Oedema	• Diuretics, supportive measures
• Fluid retention (pleural effusion, pericardial effusion, oedema, ascites)	• Diuretics, supportive measures, imatinib dosage decrease or interruption of therapy, echocardiography
• Gastrointestinal disturbances	• Administration of imatinib at mealtime and with water
• Muscle cramps, myalgia, arthralgia	• Calcium, magnesium, analgesic
• Hepatotoxicity (increase of bilirubin, hepatic enzymes)	• Interruption, dose adjustment
• Rash	• Local or systemic glucocorticoids, dosage decrease, interruption or discontinuation of therapy
Nilotinib	
• QTc interval prolongation > 480 msec	• Discontinuation. Correct serum potassium and magnesium. Check concomitant medicines. QTc < 450 msec is a prerequisite for the therapy re-initiation; follow-up ECG should be recorded after 7 days.
• Increased lipase, amylase	• Discontinuation, dose adjustment
• Hepatotoxicity (increase of bilirubin, hepatic enzymes)	• Discontinuation, dose adjustment
• Hyperglycaemia	• Glucose monitoring before and during treatment
• Hypercholesterolaemia	• Statin
• Cardiovascular complications, PAOD	• Assessment of cardiovascular risk at the initial diagnosis and during treatment.* Monitoring and management of risk factors. In case of vascular complication: therapy interruption and initiation of another TKI.
• Rash	• Local or systemic glucocorticoids, dosage decrease, interruption or discontinuation of therapy
Dasatinib	
• Pulmonary arterial hypertension	• It can develop at any time during the course of treatment, and reversible after treatment discontinuation. Baseline assessment for signs and symptoms of cardiac and pulmonary diseases.
• Fluid retention (pleural effusion, ascites, oedema, pericardial effusion)	• Diuretics, systemic glucocorticoids, dosage decrease or interruption of therapy
• Gastrointestinal disturbances	• Administration dasatinib at mealtime and with water
• Rash	• Local or systemic glucocorticoids, dosage decrease or interruption of therapy
Bosutinib	

Nonhaematological adverse events	Management
• Hepatotoxicity (increase of bilirubin, hepatic enzymes)	• Discontinuation, dose adjustment. In patients with baseline hepatic impairment the dosage should be adjusted to 200 mg/day.
• Diarrhoea Grade 3–4 (> 7 liquid stools per day)	• Discontinuation, dose adjustment
• Fluid retention (pulmonary and peripheral oedema, pleural effusion, pericardial effusion)	• Diuretics, supportive therapy
• Gastrointestinal disturbances	• Administration of bosutinib at mealtime and with water
• Rash	• Local or systemic glucocorticoids, dosage decrease, treatment interruption or discontinuation.
Ponatinib	
• Hepatotoxicity (increase of bilirubin, hepatic enzymes)	• Discontinuation, dose adjustment
• Increased lipase, symptomatic pancreatitis	• Discontinuation
• Haemorrhage (cerebral, gastrointestinal)	• Discontinuation, dose adjustment
• Cardiac arrhythmias (fainting, vertigo, chest pain, palpitations)	• Assessment of cardiovascular risk at the initial diagnosis and during treatment.* Monitoring and management of risk factors (diabetes, hypertension, hyperlipidaemia, smoking, estrogens use). In case of vascular complication: therapy discontinuation and initiation of another TKI.
• Arterial and venous thrombotic events (myocardial infarction, stroke)	• Discontinuation
• Tumour lysis syndrome	• Sufficient hydration, correction of hyperuricaemia
• Fluid retention (oedema, ascites, pleural effusion, pericardial effusion)	• Dose adjustment, discontinuation of treatment.
• Hypertension	• Antihypertensive agents (ACE inhibitors, sartans), regular blood pressure monitoring
• Rash	• Local or systemic glucocorticoids, dosage decrease, treatment interruption or discontinuation.

NG – neutrophil granulocytes, Plt – platelets, G-CSF – Granulocyte colony-stimulating factor, PAOD – peripheral artery occlusive disease; *Cardiovascular risk assessment according to the recommendations of the European Society of Cardiology (ESC) 2012.

determination of BCR-ABL1 transcript ≥ 4.5 log (expressed on IS) and delivery of results within 14 days. After treatment discontinuation, check-ups are required every month for the first 6 months, every 2 months from month 7 to month 24, and thereafter 4 times per year in patients maintaining MolR 3; ≤0.1 % IS.

- Possibility of consulting the CML centre on patient's appropriateness for treatment discontinuation, its potential hazards/risks and benefits, and development of withdrawal syndrome after TKI discontinuation.
- Immediate reinitiating of TKI therapy in case of loss of the major molecular response (MolR 3.0). Assessment of MolR every month for 6 months and every 3 months thereafter. If the major MolR is not reached within 6 months, mutational analysis is required and regular monthly molecular monitoring should be performed over the next 6 months.

3.6 Treatment in pregnancy

Results of the EUTOS population registry show that at the time of CML diagnosis about 35 % of patients are still in their reproductive period. TKIs imatinib, dasatinib and nilotinib are teratogenic and were demonstrated to cause harmful embryo-foetal effects in animal studies. Currently there are no recommendations for follow up of the patients diagnosed with CML during pregnancy; recommendations for treatment of advanced disease that develops during pregnancy are also lacking. Indeed, conception during the active TKI treatment period is discouraged.

Male CML patients. TKIs do not seem to affect male fertility or cause abortions/foetal impairment in partners of male CML patients. The general recommendation is that discontinuation of TKI therapy is not necessary in patients planning to father a baby. Experience is limited. Men may consider sperm preservation before TKI treatment, but no data are available on pre-treatment sperm quality.

Female CML patients. In women the situation is more complicated, as increased rates of abortion and foetal impairment were observed during TKI therapy. TKI treatment should be discontinued before the patient gets pregnant and it should not be initiated during pregnancy. An obstetric consultation is recommended. It is not clear how long before conception TKIs should be discontinued. TKI therapy can be reintroduced after the delivery. As TKIs are excreted in human milk, breast-feeding during the TKI therapy is contraindicated. Treatment with interferon alpha during pregnancy is safe (3–6 M units every other day, up to 5–8 M units daily), the same is true for treatment with hydroxyurea (10).

3.7 Treatment of children with CML

CML accounts for less than 3 % of all childhood leukaemias. The median age at diagnosis of CML in children is 11–12 years. About 10 % of affected children are diagnosed in advanced phase. Clear treatment recommendations are lacking. Many paediatric oncologists follow treatment guidelines for adults. Imatinib is the only TKI licensed for treatment of CML in children (10).

4 TKI adverse events and their management

TKIs mechanism of action primarily targets the *BCR-ABL1* fusion gene. As TKIs differ in their potency and, above

all, in their action on non-therapeutic target molecules involved in the biology of various organ systems, they have different adverse events profiles; these should be considered already when choosing the initial treatment (10,15,17,39). Incorrect choice of TKI can exacerbate comorbidities, such as diseases of cardiovascular system, lungs, pancreas, etc., particularly since the TKI therapy is a long-term or even lifelong treatment. Incorrect choice of TKI may also cause increased patient mortality (17,40).

All TKIs cause haematological adverse events. They lead to suppression of bone marrow function with subsequent blood cytopenias, which tend to be more pronounced at the beginning of the therapy, also because of the diminished bone marrow reserve. Later on the blood counts generally improve. Transient discontinuation of the therapy and/or dosage adjustment may be required, depending on the degree of cytopenia. Growth factors may be used. As development of cytopenias after long-term TKI treatment is uncommon, progression of the disease, MDS and other possible causes should be ruled out. Nonhaematological adverse events can manifest with skin, gastrointestinal, hepatic, pancreatic, musculoskeletal, pulmonary, metabolic or endocrine disorders. They may show as fluid retention in the body and consequent swelling. Special attention should be paid to cardiovascular complications, as they can have significant influence on patient morbidity and mortality if not managed appropriately. General symptoms, such as fatigue and headaches, are also common. During the therapy susceptibility to infections is increased. In rare cases neurological impairment or decreased

Table 9: Levels of evidence and grades of recommendation (17).

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 etc.), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

renal function may occur. Currently, no data are available on potential increase of incidence of other malignomas during the TKI therapy. Table 7 and Table 8 list the most frequent adverse events of individual TKIs and steps for their management. Levels of evidence and grades of recommendation are shown in Table 9.

TKI therapy is generally well tolerated; if adverse events do appear, they are mostly transient and self-limiting, or require only symptomatic measures. In case of higher-grade adverse events, therapy should generally be temporarily discontinued, and can be reintroduced (in the same or adjusted dose) when the adverse event resolves. Risk factors for development of complications should be recognised, their seriousness should be assessed and they should be managed as to enable therapy with the most effective TKI. Here, cooperation with professionals from other fields of medicine plays a crucial role.

In some cases, however, the drug has to be discontinued permanently, e.g. after development of pulmonary arterial hypertension during dasatinib therapy, or of PAOD during nilotinib therapy, and the patient should be switched to another TKI. In addition to clinical monitoring for adverse events, laboratory tests (electrolytes, glucose, renal function, liver function, pancreatic enzymes, lipid profile), ECG, and, sometimes, morphological investigations (e.g. chest X-rays, echocardiography, ultrasound assessment of the pleural space) are also recommended for organ damage assessment.

5 Conclusion

Rigorous following of the guidelines is extremely important for good treatment results. The key step is individualised initial assessment of predicted outcome (prognosis) of CML itself and of any comorbidities, with consequent choice of the most appropriate TKI considering the adverse events profile. Harmonised patient management, involving haematologists and selected doctors and specialists from other fields who manage comorbidities, provides better possibilities for effective integrated patient care, prevention of treatment-related complications and premature death.

Patients should be informed of their disease and its treatment, they should be familiar with symptoms and signs of possible adverse events, and should be acquainted with the necessary measures to be taken if any adverse events occur. It is also important to encourage patients to adopt healthy lifestyle. In this respect, patients' associations play an important and advantageous role in raising awareness of all aspects of the disease.

References

1. Preložnik Zupan I. Kronična mieloična levkemija. In: Košnik M, ur. Interna medicina: univerzitetni učbenik. 5. izd. Ljubljana: Littera picta; Slovensko medicinsko društvo; 2017.
2. Apperley JF. Chronic myeloid leukaemia. Lancet. 2015 Apr;385(9976):1447–59. https://doi.org/10.1016/S0140-6736(13)62120-0 PMID:25484026
3. Sawyers CL. Chronic myeloid leukemia. N Engl J Med. 1999 Apr;340(17):1330–40. https://doi.org/10.1056/NEJM199904293401706 PMID:10219069
4. Hehlmann R, Berger U, Pfirrmann M, Heimpel H, Hochhaus A, Hasford J et al. Drug treatment is superior to allografting as first-line therapy in chronic myeloid leukemia. Blood. 2007 Jun;109(11):4686–92. https://doi.org/10.1182/blood-2006-11-055186 PMID:17317858
5. Preložnik Zupan I, Pajič T, Glaser M, Grmek Zemljič T, Grat M, Fikfak N, et al. Uspešnost zdravljenja KML v Sloveniji v obdobju inhibitorjev tirozinske kinaze. Zdrav Vestn Suppl. 2012;81:II56-64.
6. Preložnik Zupan I, Pajic T, Glaser M, Grmek-Zemljic T, Grat M, Fikfak N et al. Epidemiološki podatki bolnikov s kronično mieloično levkemijo v Sloveniji. Zdrav Vestn. 2008;77(1):51–5.

7. Van Etten RA. Clinical manifestations and diagnosis of chronic myeloid leukemia [2017 Sept]. Available from: https://www.uptodate.com/
8. Negrin RS, Schiffer CA. Overview of the treatment of chronic myeloid leukemia [2017 Sept]. Available from: https://www.uptodate.com./
9. Združenje hematologov Slovenije, Preložnik Zupan I, Pajič T. Smernice za odkrivanje in zdravljenje kronične mieloične levkemije. Zdrav Vestn Suppl. 2008;77:I5–10.
10. Leukemia CM. version 2.2017, National Comprehensive Cancer Network (NCCN). [2017 Sept]. Available from: http://www.nccn.org/
11. Wang W, Cortes JE, Tang G, Khoury JD, Wang S, Bueso-Ramos CE et al. Risk stratification of chromosomal abnormalities in chronic myelogenous leukemia in the era of tyrosine kinase inhibitor therapy. Blood. 2016 Jun;127(22):2742–50. https://doi.org/10.1182/blood-2016-01-690230 PMID:27006386
12. Burmeister T, Reinhardt R. A multiplex PCR for improved detection of typical and atypical BCR-ABL fusion transcripts. Leuk Res. 2008 Apr;32(4):579–85. https://doi.org/10.1016/j.leukres.2007.08.017 PMID:17928051
13. Quintás-Cardama A, Cortes J. Molecular biology of bcr-abl1-positive chronic myeloid leukemia. Blood. 2009 Feb;113(8):1619–30. https://doi.org/10.1182/blood-2008-03-144790 PMID:18827185
14. Jabbour E, Kantarjian H. Chronic myeloid leukemia: 2014 update on diagnosis, monitoring, and management. Am J Hematol. 2014 May;89(5):547–56. https://doi.org/10.1002/ajh.23691 PMID:24729196
15. Baccarani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood. 2013 Aug;122(6):872–84. https://doi.org/10.1182/blood-2013-05-501569 PMID:23803709
16. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016 May;127(20):2391–405. https://doi.org/10.1182/blood-2016-03-643544 PMID:27069254
17. Hochhaus A, Saussele S, Rosti G, Mahon FX, Janssen JJ, Hjorth-Hansen H et al.; ESMO Guidelines Committee. Chronic myeloid leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul;28 suppl_4:iv41–51.
18. Söderlund S, Dahlén T, Sandin F, Olsson-Strömberg U, Creignou M, Dreimane A et al. Advanced phase chronic myeloid leukaemia (CML) in the tyrosine kinase inhibitor era - a report from the Swedish CML register. Eur J Haematol. 2017 Jan;98(1):57–66. https://doi.org/10.1111/ejh.12785 PMID:27428357
19. Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood. 1984 Apr;63(4):789–99. PMID:6584184
20. Hasford J, Pfirrmann M, Hehlmann R, Allan NC, Baccarani M, Kluin-Nelemans JC et al.; Writing Committee for the Collaborative CML Prognostic Factors Project Group. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. J Natl Cancer Inst. 1998 Jun;90(11):850–8. https://doi.org/10.1093/jnci/90.11.850 PMID:9625174
21. Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood. 2011 Jul;118(3):686–92. https://doi.org/10.1182/blood-2010-12-319038 PMID:21536864
22. Pfirrmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G et al. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. Leukemia. 2016 Jan;30(1):48–56. https://doi.org/10.1038/leu.2015.261 PMID:26416462
23. Fabarius A, Kalmanti L, Dietz CT, Lauseker M, Rinaldetti S, Haferlach C et al.; SAKK and the German CML Study Group. Impact of unbalanced minor route versus major route karyotypes at diagnosis on prognosis of CML. Ann Hematol. 2015 Dec;94(12):2015–24. https://doi.org/10.1007/s00277-015-2494-9 PMID:26385387
24. Cross NC, White HE, Colomer D, Ehrencrona H, Foroni L, Gottardi E et al. Laboratory recommendations for scoring deep molecular responses following treatment for chronic myeloid leukemia. Leukemia. 2015 May;29(5):999–1003. https://doi.org/10.1038/leu.2015.29 PMID:25652737
25. Baccarani M, Saglio G, Goldman J, Hochhaus A, Simonsson B, Appelbaum F et al.; European LeukemiaNet. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood. 2006 Sep;108(6):1809–20. https://doi.org/10.1182/blood-2006-02-005686 PMID:16709930
26. Drucker BJ, Guilhot F, O'Brien SG. Five-year follow-up of imatinib therapy for newly diagnosed chronic myeloid leukemia in chronic-phase shows sustained responses and high overall survival. N Engl J Med. 2006;355:2404–17.
27. Soverini S, Hochhaus A, Nicolini FE, Gruber F, Lange T, Saglio G et al. BCR-ABL kinase domain mutation analysis in chronic myeloid leukemia patients treated with tyrosine kinase inhibitors: recommendations from an expert panel on behalf of European LeukemiaNet. Blood. 2011 Aug;118(5):1208–15. https://doi.org/10.1182/blood-2010-12-326405 PMID:21562040
28. Lee SE, Choi SY, Bang JH, Kim SH, Jang EJ, Byeun JY et al. The long-term clinical implications of clonal chromosomal abnormalities in newly diagnosed chronic phase chronic myeloid leukemia patients treated with imatinib mesylate. Cancer Genet. 2012 Nov;205(11):563–71. https://doi.org/10.1016/j.cancergen.2012.09.003 PMID:23111092
29. O'Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F et al.; IRIS Investigators. Imatinib compared with interferon and low-dose cytarabine for newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med. 2003 Mar;348(11):994–1004. https://doi.org/10.1056/NEJMoa022457 PMID:12637609

30. Kantarjian HM, Shah NP, Cortes JE, Baccarani M, Agarwal MB, Undurraga MS et al. Dasatinib or imatinib in newly diagnosed chronic-phase chronic myeloid leukemia: 2-year follow-up from a randomized phase 3 trial (DASISION). Blood. 2012 Feb;119(5):1123–9. https://doi.org/10.1182/blood-2011-08-376087 PMID:22160483
31. Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW et al. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. Leukemia. 2012 Oct;26(10):2197–203. https://doi.org/10.1038/leu.2012.134 PMID:22699418
32. Saussele S, Krauss MP, Hehlmann R, Lauseker M, Proetel U, Kalmanti L et al.; Schweizerische Arbeitsgemeinschaft für Klinische Krebsforschung and the German CML Study Group. Impact of comorbidities on overall survival in patients with chronic myeloid leukemia: results of the randomized CML study IV. Blood. 2015 Jul;126(1):42–9. https://doi.org/10.1182/blood-2015-01-617993 PMID:25918346
33. Baccarani M, Pane F, Rosti G, Russo D, Saglio G. Chronic myeloid leukemia: room for improvement? Haematologica. 2017 Jul;102(7):1131–3. https://doi.org/10.3324/haematol.2017.166280 PMID:28655808
34. Padula WV, Larson RA, Dusetzina SB, Apperley JF, Hehlmann R, Baccarani M et al. Cost-effectiveness of tyrosine kinase inhibitor treatment strategies for chronic myeloid leukemia in chronic phase after generic entry of imatinib in the United States. J Natl Cancer Inst. 2016 Mar;108(7):djw003. https://doi.org/10.1093/jnci/djw003 PMID:26944912
35. Kralj E, Žakelj S, Trontelj J, Pajič T, Preložnik Zupan I, Černelč P et al. Monitoring of imatinib targeted delivery in human leukocytes. Eur J Pharm Sci. 2013 Sep;50(1):123–9. https://doi.org/10.1016/j.ejps.2013.04.026 PMID:23643738
36. Eliasson L, Clifford S, Barber N, Marin D. Exploring chronic myeloid leukemia patients' reasons for not adhering to the oral anticancer drug imatinib as prescribed. Leuk Res. 2011 May;35(5):626–30. https://doi.org/10.1016/j.leukres.2010.10.017 PMID:21095002
37. Zabriskie MS, Eide CA, Tantravahi SK, Vellore NA, Estrada J, Nicolini FE et al. BCR-ABL1 compound mutations combining key kinase domain positions confer clinical resistance to ponatinib in Ph chromosome-positive leukemia. Cancer Cell. 2014 Sep;26(3):428–42. https://doi.org/10.1016/j.ccr.2014.07.006 PMID:25132497
38. Jain N, van Besien K. Chronic myelogenous leukemia: role of stem cell transplant in the imatinib era. Hematol Oncol Clin North Am. 2011 Oct;25(5):1025–48. https://doi.org/10.1016/j.hoc.2011.09.003 PMID:22054733
39. Povzetek glavnih značilnosti zdravila Tasigna [2017 Oct]. Available from: https://ec.europa.eu/health/documents/community-register/2017/20170524137917/anx_137917_sl.pdf
40. Steegmann JL, Baccarani M, Breccia M, Casado LF, García-Gutiérrez V, Hochhaus A et al. European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia. Leukemia. 2016 Aug;30(8):1648–71. https://doi.org/10.1038/leu.2016.104 PMID:27121688