Recommendations for Treating People Living with CML

A patient-friendly summary of the European LeukemiaNet 2020 recommendations for treating chronic myeloid leukemia

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Foreword by the Workgroup

Chronic Myeloid Leukemia (CML) is a rare cancer of the blood and bone marrow. CML is a type of leukemia which begins in the stem cells of the bone marrow. Stem cells normally mature into any of the three major blood cell lines: white blood cells, red blood cells or platelets. When stem cells become abnormal and too many white blood cells are produced, then CML starts. Over time, CML cells replace normal cells in the bone marrow which prevents the bone marrow from making healthy blood cells. As the disease progresses, the number of normal white blood cells decreases.

There are three stages of CML:

Chronic phase (CP) – This is the initial stage where the body produces too many white blood cells. This phase may last months to years. If symptoms appear, they are likely to be mild and easily missed.

Accelerated phase (AP) – If left untreated, the CML cells might undergo more biological changes and the disease might progress to a more advanced stage.

Blast phase (BP) – In this phase, there are 20% or more immature leukemia (cancer) cells called blasts in the blood or bone marrow, the disease worsens and the patient generally feels unwell.

In humans, each cell normally contains 22 pairs of chromosomes and two sex chromosomes (XX or XY). Each chromosome contains thousands of genes. In CML cells, part of chromosome 9 joins together with part of chromosome 22. This leads to the formation of the so-called Philadelphia (Ph) chromosome. As a result, part of a gene called *ABL1* that is normally found on chromosome 9 joins part of a gene called *BCR* located on chromosome 22. The result is an abnormal gene called *BCR-ABL1* on chromosome 22. This gene controls the production of a protein which has the function of a tyrosine kinase. Tyrosine kinases normally help cells to divide and multiply. However, the abnormal gene makes a tyrosine kinase which produces too many white blood cells. Treatment aimed at blocking this abnormal tyrosine kinase activity has revolutionized the treatment of CML.

The **European LeukemiaNet (ELN)**, a publicly funded research network, provided treatment **recommendations for treating CML** first in 2006 followed by updates in 2009, 2013 and again in 2020. The current recommendations for adult CML patients were agreed by 34 CML experts from Europe, America and Asia-Pacific, based on the best available scientific data at the time of publication. ELN prepared the recommendations for doctors and patients to improve the understanding of CML.

The 2020 update of the ELN recommendations reflects the fact that new treatment options are available. In particular, the first generic formulation of a tyrosine kinase inhibitor (TKI) has been approved for CML. A new long-term survival score (ELTS) has also been introduced and new risk factors have been identified. Diagnostic tests are now described in more detail. Monitoring of treatment response by quantitative polymerase chain reaction (PCR) is recommended, whenever possible. Stopping treatment and achieving treatment-free remission (TFR) can be considered as a goal for eligible patients who have access to frequent, high-quality molecular monitoring. New recommendations are also available now for family planning.

We have summarized the ELN recommendations for you which you can use to discuss your disease and treatment choices with your doctor. The summary was prepared by the following workgroup of patient advocates:

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Introduction

The treatment of chronic myeloid leukemia (CML) has changed in recent years. CML has evolved from a life-threatening cancer to a manageable disease. Most patients can benefit from a highly effective class of drugs called tyrosine kinase inhibitors (TKI). Several TKIs are available today. However, treatment is expensive and may lead to complications. Therefore, the disease should be managed by doctors who are specially trained to treat each patient's specific needs.

Many patients with chronic phase CML respond well to treatment and reach nearly normal life expectancy. Some patients are able to reach a stable deep molecular response (DMR). These patients may also be eligible to stop taking TKIs and continue their lives free of medication. This is called treatment-free remission (TFR). This treatment goal may only be available to few patients who have access to effective drugs and quality monitoring. For most patients, the main goals of treatment include achieving major molecular response (MMR) and normal survival.

Diagnostic procedures

Several tests and examinations are done to confirm whether a patient has CML. These include:

- **Physical examination** – Your doctor examines you, especially for the size of your spleen and your liver. If you have CML, then your spleen might be enlarged.
- **Complete blood count** – Blood is taken from your arm vein to assess for different types of blood cell and their amounts.
- **Cytologic and cytogenetic testing** – A bone marrow cell sample **(bone marrow aspirate)** is removed using a hollow needle. This test allows the doctor to determine the form and function of blood cells in your bone marrow and the stage of your CML. A small piece of bone may also be taken by your doctor to check for blast cells **(bone marrow biopsy)**. The presence of blast cells in this bone sample indicate that the patient might be at higher risk. Bone marrow cells are evaluated using cytogenetic testing. **Chromosome banding analysis (CBA)** is recommended to detect the Philadelphia chromosome and other chromosome abnormalities which indicate higher risk patients. Another test known as **fluorescence in-situ hybridization (FISH)** should be carried out if *BCR-ABL1* (gene for CML) has been identified but the Philadelphia chromosome cannot be detected by other cytogenetic tests and if qualitative PCR is not available.
- **Qualitative polymerase chain reaction (PCR)** – This highly sensitive test detects *BCR-ABL1* in your blood or bone marrow. This test must be done at the time of CML diagnosis. Thereafter, the quantitative PCR test is used. The quantitative test results serve as reference values and are used to assess changes in the amount of *BCR-ABL1* to help ensure your treatment is effective.
- **Electrocardiogram (ECG)** – Electrical signals in your heart are recorded to check for heart disease and abnormalities in the signal transduction in the heart.
- **Biochemical blood profile** – Standard tests are carried out on a blood sample taken from your vein. The results are then compared with standard values which show a healthy status.

Your doctor may also ask you to undergo other diagnostic procedures. This will depend on your own medical characteristics, your medical history, and any other diseases that you might have.

CML in different populations (epidemiology)

CML might affect anybody in any age group. In Western countries, patients are on average older (over 50 years). In Africa or Asia, CML is more common in younger age groups including children and adolescents.

Age plays an important role in the management of CML and should be considered when making treatment decisions. Older patients are more likely to receive treatment for other diseases. In younger patients, family planning and issues regarding pregnancy are key treatment considerations.

Prognostic factors at the time of diagnosis

At the time of CML diagnosis, your age, the size of your spleen, and other measurements such as blood cell counts can influence how you may respond to treatment with TKIs. These prognostic factors should be assessed before you start any drug treatment. Prognostic factors are used to calculate a patient's relative risk score. Knowing your risk score helps you and your doctor to choose the best treatment.

Three prognostic systems have been used to calculate the risk of disease progression and to assess survival with CML: Sokal, Euro, and EUTOS. A fourth system, the more specific long-time survival ELTS score, was developed in 2016. The ELN experts recommend using the new score instead of the older ones. The ELTS score does not consider deaths which are unrelated to CML, rather it focusses on the risk of dying from CML. This is because most patients today have a near normal life expectancy and do not die from CML.

Other prognostic factors present at the time of your CML diagnosis may also influence your outcome and should be carefully monitored. These factors include fibrosis content in your bone marrow aspirate sample and additional chromosome changes (so-called additional chromosome aberrations or ACA) in cells with the Philadelphia chromosome.

Definitions of response

The goal of TKI treatment is to achieve disease remission. In CML, response to treatment is evaluated by measuring the amounts of the *BCR-ABL1* copies (also called transcripts). There are different levels of response:

- **Complete hematologic response (CHR)** — Blood cell count has returned to normal. Blood tests do not show any immature white blood cells. Also, if initially enlarged, the spleen has returned to a normal size.
- **Complete cytogenetic response (CCyR)** — Cytogenetic analysis of bone marrow cells does not show any cells carrying the Philadelphia chromosome in at least 20 metaphases (metaphase is a stage in the process of cell division).
- **Major molecular response (MMR)** — The quantitative PCR test can still detect the presence of *BCR-ABL1*, but at a lower level (below 0.1%). This is considered an excellent response.
- **Deep molecular response (MR4 or MR4.5)** — The PCR test can still detect *BCR-ABL1*, but at a very low level, close to the lowest limit of detection (*BCR-ABL1* below 0.01% for MR4 and below 0.0032% for MR4.5). Some laboratories that can't detect *BCR-ABL1* at these low levels describe the disease as being molecularly undetectable. Testing laboratories should state the sensitivity of their PCR test. *BCR-ABL1 l*evels as low as ≤ 0.001% can be detected (see Table 1).

Molecular response is measured in a standardized manner according to the International Scale (IS). The testing laboratory will assess the number of *BCR-ABL1* copies in relation to the number of copies of a reference gene as shown in Table 1 (the ABL1 as a control gene or other internationally accepted control gene copies such as the gene GUSB).

Table 1.

	MMR	MR^4	$MR^{4.5}$	MR^5
Minimum number of reference gene copies in the sample	10,000 ABL1 or 24,000 GUSB	10,000 ABL1 or 24,000 GUSB	32,000 ABL1 or 77,000 GUSB	100,000 ABL1 or 240,000 GUSB
BCR-ABL1 reference gene copies on the International Scale as percent	≤ 0.1%	≤ 0.01%	≤ 0.0032%	≤ 0.001%

≤ means less than or equal to

Monitoring, response to treatment and milestones

Your doctor will monitor your response to treatment with a TKI by doing tests (as shown in Table 2). Some patients respond and their treatment is continued. Other patients do not respond optimally to treatment or may become resistant to their TKI and need a treatment change. Finally, some patients may need a treatment change because they do not tolerate their drug.

In many countries, high-quality molecular testing is available. Cytogenetic testing is no longer needed to monitor response after complete cytogenetic remission has been achieved. Quantitative PCR should be used whenever possible to count the amounts of *BCR-ABL1* in the blood.

Table 2.

Blood tests	Every 2 weeks until complete hematologic response is achieved. More frequent testing may be needed in certain cases.
Molecular testing	**Quantitative PCR**: At least every 3 months even after MMR is reached and confirmed. More frequent testing may be needed in certain cases.
Cytogenetic testing	**Chromosome banding analysis (CBA)**: Should be carried out only in patients with an unusual exchange of genetic material between chromosomes (so-called atypical translocations), with rare or unusual *BCR-ABL1* copies that cannot be assessed by quantitative PCR, to rule out additional chromosomal abnormalities in patients who do not respond or are resistant to treatment, or in patients who progress to accelerated or blast phase. **Fluorescence in situ hybridization (FISH)**: May be needed in patients with unusual *BCR-ABL1* fusion transcripts.

Patients who have reached MMR have achieved an excellent response. However, being in remission is not the same as being cured. Even if tests cannot find any trace of CML in your cells, the disease may return. This is why monitoring is very important. Your treatment may need to be continued or even changed.

The following monitoring milestones are used to assess the effectiveness of your treatment:

- **Optimal response** means that your treatment leads to a reduction in the amount of BCR-ABL1 as shown in Table 3. Your current treatment should be continued.
- **Warnings** are signs that your disease isn't responding to treatment as expected. Your doctor may check you more frequently to decide if you need a change in treatment.
- **Failure** means that your treatment is unlikely to be effective. You and your doctor should discuss the possible options of switching treatment.

Table 3 shows monitoring milestones and response levels in CML.

Table 3.

Time	Optimal response	Warnings	Failure
At diagnosis	Does not apply at this stage	High-risk additional chromosome aberrations (ACA) in cells with the Philadelphia chromosome High risk by ELTS score	Does not apply at this stage
At 3 months	*BCR-ABL1* ≤10% in PCR test	*BCR-ABL1* >10% in PCR test	*BCR-ABL1* >10% in PCR test if confirmed within 1–3 months
At 6 months	*BCR-ABL1* ≤1% in PCR test	*BCR-ABL1* >1–10% in PCR test	*BCR-ABL1* >10% in PCR test
At 12 months	*BCR-ABL1* ≤0.1% in PCR test	*BCR-ABL1* >0.1–1% in PCR test	*BCR-ABL1* >1% in PCR test
Then, and at any time during treatment	*BCR-ABL1* ≤0.1% in PCR test*	*BCR-ABL1* >0.1–1% in PCR test Loss of ≤0.1% (MMR)*	*BCR-ABL1* >1% in PCR test Resistance mutations High-risk additional chromosome aberrations (ACA) in cells with the Philadelphia chromosome

* Loss of MMR (*BCR-ABL1* level >0.1%) also indicates failure after TFR.

In patients attempting TFR, the optimal response (at any time) is *BCR-ABL1* ≤0.01% (MR^4).

A change of treatment may be considered if you have not achieved MMR after 36 to 48 months of treatment.

Currently available CML treatments

The ELN makes specific recommendations for the treatment of CML. Choice of treatment is based on your personal disease status and depends on your CML at diagnosis. Your doctor also evaluates your risk score, your overall health, and other medical conditions. Your treatment goals are considered in determining the best therapy for you but this could differ from the ELN recommendations. Your doctor may also have to consider whether some drugs are available and if the drugs are affordable.

Treatment goals can change over time. For some patients, normal survival or good quality of life with only few or mild side effects might be the treatment goals. In other patients, achieving stable deep molecular response and stopping medication might be the desired goals.

CML treatments are defined according to the order that they are usually prescribed: first line (given as the first treatment line after diagnosis), second line, third line, fourth line and fifth line.

First-line treatment

Patients with symptoms of CML or high levels of white blood cells can be treated with hydroxyurea for a short time until the diagnosis of CML is confirmed by genetic testing. Hydroxyurea is a chemotherapy taken by mouth that reduces the number of white blood cells. Hydroxyurea can be used before starting first-line treatment for CML with a TKI.

TKIs work by blocking the activity of BCR-ABL1 tyrosine kinase. *BCR-ABL1* is the gene that causes CML. TKIs can reduce the disease to a minimum, restore health and a good quality of life. Some patients even reach undetectable *BCR-ABL1* levels that allow them to stop TKI treatment.

Several TKIs have been approved for first-line treatment and are available in most countries. The optimal choice of a TKI is guided by the health profile of the patient and treatment goals based on shared decision making between patient and doctor. All TKIs are not permitted (contraindicated) during pregnancy.

Imatinib (Glivec® or Gleevec® or generic imatinib)

Imatinib was the first TKI to be used to treat CML. This is why it is called a first-generation TKI. Imatinib is also a first-line CML treatment. Therapy with imatinib results in good treatment responses and normal life expectancy in most CML patients. After 1 year of treatment, about 20% to 60% of patients reached an MMR and after 5 years of treatment around 60% to 80% reached an MMR. Some 35% to 70% of patients are likely to achieve a DMR (MR^4 or deeper) after 5 years. Overall, between 90% and 95% of patients survived after 5 years and up to 85% were alive after 10 years.

The standard dose in chronic phase CML is 400 mg once daily but may be reduced to 300 mg if an optimal response is achieved and imatinib is not well tolerated. A dose of 400 mg twice daily can be considered in patients diagnosed with accelerated phase. Patients who progress to a more advanced phase while on imatinib should be switched to a second-generation TKI. In patients who reach an MMR with imatinib, the dose can be lowered (see Table 4).

There have been no reports in patients treated with imatinib which contraindicate its use and life-threatening complications are unknown. However, patients with poor heart or kidney function should be monitored closely. Muscle cramp and a feeling of tiredness (fatigue) may affect some patients using imatinib. Water building up in the body, gastrointestinal symptoms, joint pain and skin rash have also been reported. These symptoms may resolve after some time or after patients interrupt taking imatinib for a while.

Dasatinib (Sprycel®)

Dasatinib was developed after imatinib, has a different biochemical profile and is therefore called a second-generation TKI. Dasatinib can be used as a first-line treatment for CML. It has a stronger action than imatinib and may lead to a faster and deeper response while patient survival is similar. Dasatinib is also effective against certain mutations that are resistant to imatinib.

The approved dose is 100 mg once daily in the chronic phase of CML and 70 mg twice daily in advanced phase CML. Some patients have even reached a good treatment response with doses as low as 50 mg with fewer side effects.

Dasatinib may injure the lungs and the lining of the lungs (pleuro-pulmonary toxicity) and should not be used as first-line treatment in patients who have lung or heart disease. These complications may also occur after chronic therapy with dasatinib. Other side effects with dasatinib are generally similar to imatinib.

Nilotinib (Tasigna®)

Your doctor could also prescribe nilotinib, another second-generation TKI used as a first-line treatment. Like dasatinib, nilotinib leads to a faster and deeper response than imatinib while patient survival is similar. Nilotinib is also effective against some mutations that are resistant to imatinib.

Nilotinib is approved at a dose of 300 mg twice daily for first-line therapy. In second-line and more advanced treatment lines after resistance to first line therapy, the dose is 400 mg twice daily. These higher doses have led to cardiovascular side effects and should be used carefully.

You should not use nilotinib as first-line treatment if you have heart disease, any cardiovascular problems or inflammation of the pancreas. Patients with high blood pressure, high cholesterol levels or diabetes mellitus should use nilotinib carefully. Cardiovascular side effects tend to occur more with nilotinib than with imatinib.

Bosutinib (Bosulif®)

Another option for first-line CML treatment with a second-generation TKI is bosutinib. Like dasatinib and nilotinib, bosutinib has a stronger action and may lead to a faster and deeper response than imatinib. Bosutinib can also be prescribed in patients who have mutations resistant to imatinib.

The approved dose of bosutinib is 400 mg once daily as first-line treatment and 500 mg once daily if used as second-line therapy. Higher doses are not recommended. Lower doses may be used if patients experience side effects and the response to treatment is optimal.

Diarrhea affects nearly one in three patients starting bosutinib but usually disappears with time. Markers of liver inflammation may be increased at the beginning of treatment.

Radotinib (Supect®)

The second-generation TKI radotinib is available as a first-line treatment only in South Korea. A significantly higher molecular response has been seen with radotinib at a dose of 300 mg twice daily than is achieved with imatinib. Liver function test values are often increased with radotinib.

Interferon alpha (IFNα)

Before imatinib was introduced, interferon alpha (IFNα) was the best available treatment for CML. Interferon alpha activates the immune system against CML cells. Today, improved formulations of interferon alpha known as pegylated interferon (PEG-IFNα) are available. Various combinations of PEG-IFNα with a TKI are being evaluated in patients to reach a faster and deeper molecular response and increase the number of patients eligible for stopping treatment.

Generics

A generic formulation of imatinib is now available worldwide and generic dasatinib is expected to become available soon. Generic TKIs are less expensive than the original TKI products and, therefore, more affordable to patients. Lower costs of medicines may improve drug compliance, especially for patients who have to pay for their medication.

Generic TKIs are an acceptable alternative to the original TKI as long as the same quality has been demonstrated. Dosing of the generic should be the same as for the original TKI. Switching a patient from original to generic drug requires more frequent molecular monitoring and assessment of side effects for up to 6 months. This is to ensure the treatment is effective and safe. Thereafter, response monitoring should be the same as for the original TKI. Ideally, CML patients should not switch between different generic products with the same active substance.

TKI costs and cost effectiveness

Most patients with CML will continue to take a TKI for life. Cost effectiveness of treatment is an important consideration when choosing the right TKI. Studies have shown that generic imatinib is a cost-effective initial treatment for chronic phase CML.

Second-line treatment

Second-line treatment is treatment for a disease or condition after use of the initial treatment (first-line treatment). You and your doctor may make a decision to change your initial first-line TKI to another second-line TKI. This is not unusual and such a decision could be made for the following reasons:

- Failure or resistance: your current treatment must be changed and the presence of mutations checked
- Intolerance and treatment-related complications: a treatment change can be considered for these reasons and also regarding the response to treatment
- Warning: continuation or change of your treatment should be considered based on an insufficient response, individual patient features, and tolerance

Imatinib, dasatinib, nilotinib, and bosutinib can all be used as second-line treatment options after intolerance at the doses described above. For treatment after resistance the appropriate dose might be different. The same treatment response definitions are also used. There are no studies comparing the TKIs with each other and the choice of TKI is patient-related. Therefore, the ELN does not recommend the use of any specific second-generation TKI unless patients have a *BCR-ABL1* mutation. Treatment options in case of specific mutations are shown in Table 5. For second-line treatment, all patients should continue treatment with a TKI in the acute, blast or chronic phases of CML. Patients in chronic phase who do not reach cytogenetic response should continue taking their TKI if no other options are available. Continued treatment appears to improve survival in these patients.

Treatment beyond second line

Treatment options may still be available for patients who do not respond to two or more TKIs. However, survival may not be optimal in patients with a *BCR-ABL1* level >1% or those who do not reach a complete cytogenetic response. The choice of a TKI depends on the patient's *BCR-ABL1* mutations. Ponatinib is the only TKI that is effective for one specific mutation (T315I). Stem cell transplantation should be considered as a treatment option for CML in patients who do not respond adequately to two or more TKIs.

Ponatinib (Iclusig®)

Ponatinib is the drug with the strongest action among all approved BCR-ABL1 TKIs. You may receive ponatinib, a third-generation TKI, as third-line therapy if you do not respond to two other TKIs. You may also be given ponatinib if you have the genetic mutation called T315I. This mutation may cause resistance to all other drugs except ponatinib. However, your doctor might consider that ponatinib is not suitable for you if you have any cardiovascular problems.

The approved starting dose of ponatinib is 45 mg once daily. Cardiovascular side effects have occurred with ponatinib and these happen more frequently as the dose is increased. The ELN therefore recommends starting treatment at a lower dose of 30 mg or 15 mg in patients with cardiovascular risks. The dose is only increased if urgently needed. For patients who have achieved a treatment response, the daily dose has also been reduced to 15 mg.

A brief summary of the choice of TKI for CML in chronic phase is shown in Table 4.

Table 4.

Line of treatment	Which patients?	Which treatment?
1st line*	All patients	**Imatinib** 400 mg once daily or lower if MMR achieved 300 mg once daily if poorly tolerated **Dasatinib** 100 mg once daily or possibly a dose as low as 50 mg once daily **Nilotinib** 300 mg twice daily **Bosutinib** 400 mg once daily or lower dose if not tolerated **Radotinib** 300 mg twice daily (only in South Korea)
2nd line	Treatment failure or resistance	**Any TKI** not used 1st line, guided by *BCR-ABL1* mutation analysis**: for example, F317L/V/I/C, T315A with **nilotinib** 400 mg twice daily or **bosutinib** 500 mg once daily
	Intolerance and side effects	**Any TKI** not used 1st line, choice depends on patient and treatment response. Doses may need to be adapted.
3rd line and later lines	Treatment failure or resistance	**Any TKI** not used 1st line, guided by *BCR-ABL1* mutation analysis: for example, T315I with **ponatinib** 45 mg once daily or lower dose if poorly tolerated; lower dose after initial response; ponatinib also preferred when 1st and 2nd line have failed and no specific mutations are present.
	Poor response to 2 or more TKIs	Consider stem cell transplantation

* Hydroxyurea is given to symptomatic patients pending CML confirmation, IFNα in combination with TKIs is a recent approach to 1st line CML treatment

** See Table 5 for all specific mutations

Toxicity, side-effects, and complications

Like all drugs, treatment with TKIs results in unwanted side effects and complications otherwise known as adverse events. Your doctor will consider these adverse events, your overall health and your CML status when choosing a TKI for you. According to ELN, the following types of adverse events should be considered:

1. Hematologic adverse events such as abnormal decreases in blood counts (neutropenia, thrombocytopenia, and anemia). These changes typically occur during the first phase of treatment. You may have to reduce your dose for a while but changing your TKI is usually not needed.
2. Non-hematologic adverse events:
   - "Side effects" that affect how you tolerate the treatment and impair your quality of life. About 30% of patients need to change their treatment due to these side effects.
   - Changes that affect your health and quality of life or even lead to death may be called "complications". As many as 15% of patients require a treatment change due to these complications.

As with all drugs, the use of any TKI can result in toxicity, however, not comparable to that of chemotherapy. Toxicities cause complications which are relevant when choosing the right TKI for each patient. If you have or have had a certain disease or condition, then this may be a reason not to give you a specific TKI.

For example, disease of the arteries (cardiovascular disease) is a strong contraindication to using nilotinib first line and ponatinib second or third line, unless there is no other treatment option. Poor oxygen supply (respiratory failure) and lung disease (pleuro-pulmonary disease) are strong contraindications to dasatinib first line. Imatinib should not be given to patients with significant kidney problems (renal impairment). No other strong contraindications to imatinib or bosutinib are currently known.

The risk of blockage of the arteries (arterial occlusive disease) is highest with ponatinib, followed by nilotinib, and a lot lower with other TKIs.

Water building up around the lungs (pleural effusion) mainly occurs with dasatinib.

Diarrhea or constipation may occur with any TKI. Diarrhea is seen especially with bosutinib, but this usually resolves. Problems may be fewer with a dose of 400 mg of bosutinib once daily and the use of loperamide may help prevent or treat symptoms.

Blood sugar may be increased (hyperglycemia) mainly with nilotinib and should be monitored closely. High blood cholesterol may also occur with nilotinib.

Toxicity of the liver (hepatotoxicity) may be caused by any TKI, but mainly occurs with bosutinib and nilotinib. Usually, only markers of inflammation are increased without any serious liver injury.

Reductions in blood cell counts (cytopenia) occur with all TKIs during the first few weeks of therapy. These effects can usually be managed with supportive care.

Nilotinib and bosutinib can result in an increase of a protein called lipase. Sometimes, this can lead to inflammation of the pancreas, and another TKI is then preferred.

Treatment options for resistant *BCR-ABL1* mutations

Experience with first-line treatment in patients with CML shows that 10% to 15% of patients are resistant to imatinib and less than 10% of patients are resistant to a second-generation TKI. Resistance means that a satisfactory treatment response is not being achieved. Resistance may occur because patients do not take their treatment as prescribed or that they have a specific *BCR-ABL1* mutation which does not respond to the TKI. Mutations are the reason for resistance in one out of three resistant patients in the chronic phase and in two out of three resistant patients in the accelerated or blast phases.

Table 5 shows recommended TKIs in the case of *BCR-ABL1* resistance mutation valid for any treatment line:

Table 5.

Which mutations?	Which treatment?
Patients who have the T315I mutation	Ponatinib
Patients who have the F317L/V/I/C, T315A mutation	Nilotinib, bosutinib*, or ponatinib
Patients who have the V299L mutation	Nilotinib or ponatinib
Patients who have the Y253H, E255V/K, F359V/I/C mutation	Dasatinib, bosutinib*, or ponatinib

* Whether bosutinib can effectively treat patients with mutations, including E255V or E255K, still needs to be confirmed

Treatment of advanced-phase CML

Very few patients progress to advanced phase CML. The ELN experts recommend that doctors follow the steps in Table 6 to manage end-phase disease.

Table 6.

Recommended strategy for treating advanced phase CML	
Prevention of disease progression by eliminating *BCR-ABL1*	• Make sure that TKI treatment works well
Appearance of high-risk additional chromosomal aberrations (ACA) as a sign of early progression	• Watch closely, consider intensifying treatment by using ponatinib or stem cell transplantation
Primary blast phase	• Start with imatinib, change to a second-generation TKI based on the presence of specific mutations
Resistance to a second-generation TKI in first line or second line	• Use ponatinib unless cardiovascular risk factors are present or use a drug that is being tested in clinical studies • Consider stem cell transplantation
Failure to ponatinib	• Early stem cell transplantation is recommended as the risk of disease progression is high
Accelerated phase	• Treat patient as high risk; proceed to stem cell transplantation if response is not optimal
Progression to blast phase	• Attempt to return disease into a second chronic phase • Outcome with currently available TKI is poor (less than 1 year) • Consider adding chemotherapy • Choice of TKI should be based on previous therapy and *BCR-ABL1* mutation status • After second chronic phase is achieved proceed to stem cell transplantation without delay

Stem cell transplantation

If none of the drugs recommended for CML is effective or available, your doctor may suggest that you receive stem cells from a healthy donor. This procedure is called allogeneic stem cell transplantation (allo-SCT) and may offer a cure.

Stem cell transplantation may be a possibility for CML patients in the chronic phase who do not respond or are intolerant to two or more TKIs. In countries where life-long TKI treatment is too expensive, stem cell transplantation can be a less expensive treatment option for patients in chronic phase CML. Stem cell transplantation remains a possibility for accelerated phase patients who do not achieve optimal response and for patients in blast phase. Before receiving a stem cell transplant, patients are treated with at TKI. In uncontrolled, resistant blast phase, stem cell transplantation is not recommended. For these patients, chemotherapy and/or palliative care might be more suitable.

Quality of life

The success of TKI treatment means many patients now live almost as long as people without CML. Quality of life has become increasingly important and patient-reported outcome questionnaires have been shown to be useful in understanding the long-term challenges faced by CML patients. Additional research is needed to further improve the quality of life for all CML patients in the future.

Treatment-free remission

Patients who have responded well to treatment with TKIs and who have maintained a deep molecular response over a long period of time may no longer need TKI treatment. Some of these patients may be eligible to attempt discontinuing treatment under medical supervision. Stopping treatment in this manner is known as treatment-free remission (TFR). Importantly, some patients who are eligible for TFR prefer to continue treatment.

According to ELN recommendations, the following criteria **must** be met before stopping treatment:

- Patient is in first chronic phase of CML.
- Patient is motivated to stop treatment and communicates well.
- Patient has access to high-quality quantitative PCR with test results rapidly available.
- Patient agrees to more frequent monitoring after stopping treatment. This means monthly for the first 6 months, every 2 months for months 6–12, and every 3 months thereafter.

In addition, before stopping treatment, the following **minimal criteria** must be met:

- Patient is taking current TKI in first line or second line if intolerance was only reason for changing TKI.
- Patient has typical *BCR-ABL1* transcripts.
- Patient has received TKI for more than 5 years (or more than 4 years with a second-generation TKI).
- Patient has been in DMR (MR^4 or better) for more than 2 years.
- Patient has not had prior treatment failure.

The additional criteria for stopping treatment are considered **optimal** when:

- Patient has received TKI treatment for more than 5 years.
- Patient has been in DMR for more than 3 years if MR^4.
- Patient has been in DMR for more than 2 years if $MR^{4.5}$

Not all patients are able to maintain TFR after stopping treatment, even if all the above-mentioned criteria were met. In clinical studies, the disease recurred in about 50% of patients following TKI stop. This mostly happened within the first 6-8 months. This is why frequent molecular testing is very important during the first year of treatment stop. Although the disease rarely comes back after one year in TFR, this may still happen even much later. Patients should therefore be monitored every 3 months for life to prevent the disease progressing unnoticed. Patients with molecular recurrence can usually restart TKI treatment. Most of these patients (90%–95%) then achieve undetectable levels of disease again.

Talk to your doctor if you consider attempting TFR. Your doctor should review the potential risks and benefits with you. The final decision to stop TKI treatment should only be made jointly by you and your doctor.

Pregnancy and parenting

You may be at a stage where you are planning to have a family. And you may want to know how your disease and treatment might affect these plans.

It has become evident that men who are taking a first or second-generation TKI do not have a higher risk of abnormalities in their children. Therefore, men planning to father a child do not need to stop taking imatinib, bosutinib, dasatinib, or nilotinib. There is currently little or no data on the effects of other TKIs on sperm or offspring.

In women, however, all TKIs are contraindicated during pregnancy and should be stopped as TKIs may harm unborn children. Women are advised to discuss options for continuing or discontinuing treatment and for continuing or discontinuing pregnancy with their doctor, especially in women with more advanced disease. If needed, IFNα can be used to control CML during pregnancy. Women should not take TKIs while breast-feeding because small amounts pass into breast milk.

Women who wish to become pregnant and are eligible for TFR can stop TKI treatment. Women who lose MMR during pregnancy usually do not need to restart treatment before giving birth. Women who lose MMR before becoming pregnant should restart treatment. Once they have reached durable DMR again, they can attempt a second treatment stop and then try to become pregnant.

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