Practical management of chronic myeloid leukaemia in Belgium

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Imatinib has drastically changed the outcome of patients with chronic myeloid leukaemia, with the majority of them showing a normal life span. Recently, the development of second and third generation tyrosine kinase inhibitors and the possibility of treatment discontinuation made the management of these patients more challenging. In this review, practical management guidelines of chronic myeloid leukaemia are presented adapted to the Belgian situation in 2014. In first line chronic phase patients, imatinib, nilotinib and dasatinib can be prescribed. While second generation tyrosine kinase inhibitors give faster and deeper responses, their impact on long-term survival remain to be determined. The choice of the tyrosine kinase inhibitor depends on chronic myeloid leukaemia risk score, priority for a deep response to allow a treatment-free remission protocol, age, presence of comorbid conditions, side effect profile, drug interactions, compliance concerns and price. Monitoring the response has to be done according the 2013 European LeukemiaNet criteria, and is based on the bone-marrow cytogenetic response during the first months and on the blood molecular response. Molecular follow-up is sufficient in patients with a complete cytogenetic response. For patients who fail frontline therapy, nilotinib, dasatinib, bosutinib and ponatinib are an option depending on the type of intolerance or resistance. T315I patients are only sensitive to ponatinib, which has to be carefully handled due to cardiovascular toxicity. Advanced phase diseases are more difficult to handle, with treatments including allogeneic stem cell transplantation, which is also an option for patients failing at least two tyrosine kinase inhibitors. The possibility of treatment-free remission and pregnancy are also discussed.

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Introduction

Chronic myeloid leukaemia (CML) is a myeloproliferative neoplasm characterised by the uncontrolled proliferation of mature and maturing granulocytes. CML is associated with a genetic translocation, t(9;22), also known as the Philadelphia (Ph) chromosome. The product of this fusion gene is a constitutively active

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Table I. Staging of CML according to the ELN or WHO criteria (both can be used).[26,27]

Chronic Phase (CP)	Accelerated Phase (AP)	Blast Phase (BP)
ELN criteria None of the criteria for AP or BP	– Blasts 15 - 29% in blood or BM ; – Blasts + promyelocytes ≥ 30% in blood or BM ; – Basophilia ≥ 20% in blood; – Platelets < 100 x 10^9/L unrelated to therapy ; – Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+), major route, on treatment.	≥ 30% Blasts in blood or BM ; Extramedullary blastic infiltrates apart from spleen.
WHO criteria None of the criteria for AP or BP	– Blasts 10-19% in blood or BM ; – Persistent thrombocytopenia (< 100 × 10^9/L) unrelated to therapy – Persistent thrombocytosis (> 1000 × 10^9/L) unresponsive to therapy ; – Increasing white blood cells and spleen size unresponsive to therapy ; – Basophilia ≥ 20% in blood – Clonal chromosome abnormalities in Ph+ cells (CCA/Ph+). on treatment (clonal evolution)	≥ 20% Blasts in blood or BM ; Extramedullary blastic infiltrates apart from spleen ; Large clusters of blasts on bone marrow biopsy.
"major routes" abnormalities include : *trisomy 8, additional Ph (+der(22)t(9;22)(q34;q11) or ider(22)(q10)t(9;22)(q34;q11)), isochromosome 17, and trisomy 19.*[2]		

Table II. Initial Work up.

History	Medical history and exhaustive medication list History of cardiovascular events
Physical examination	Spleen size (cm below costal margin) in order to calculate a prognostic score Special attention to hypertension
Blood Analysis	CBC, differential count, peripheral blood smear PCR for BCR-ABL1 Electrolyte, renal and hepatic function Lipase, Amylase, TSH, glycaemia, HbA1c and lipid profile if Nilotinib considered for initial treatment ß-HCG for women of childbearing age
Bone Marrow Aspiration	Differential count Cytogenetic analysis FISH for BCR-ABL1 (if PCR for BCR-ABL1 negative)
EKG	To exclude long QT syndrome before starting Nilotinib or Dasatinib
Echocardiography	To rule out pulmonary arterial hypertension before starting Dasatinib
Chest X-ray	To exclude pleural effusion before starting Dasatinib
Abdominal Ultrasound	To evaluate spleen size if clinical assessment is not possible (obese patients)

tyrosine kinase called BCR-ABL1 which induces a cytokine-independent proliferation of CML cells. In the absence of treatment, CML has a triphasic clinical course as it progresses from a chronic phase (CP) to an accelerated phase (AP) and onto a terminal blast phase (BP – see *Table I* for definition), with a median survival of about five years before the era of tyrosine kinase inhibitors (TKIs) therapies.[1] Nowadays, imatinib, nilotinib and dasatinib, are reimbursed in Belgium for the treatment of newly diagnosed CML patients. Bosutinib and ponatinib are available in specific circumstances. Thanks to these targeted therapies, the survival of these patients has dramatically improved, transforming CML into a chronic disease.

Table III. Prognostic scores.

	Sokal (1984)[28]	Euro/Hasford (1998)[29]	EUTOS (2011)[8]
Age	x	x	
Spleen size*	x	x	x
Blasts %	x	x	
Platelet count		x	
Basophils %		x	x
Eosinophils %		x	
Online calculators	http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html	www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html	

** Distance from costal margin (cm).*

We will provide a practical review on how to manage CML patients based on the new European LeukemiaNet (ELN) guidelines.[2] These guidelines are adapted to the local situation in Belgium in 2014.

Chronic Phase (CP)

Diagnosis and risk stratification

Most of the patients in CP-CML are asymptomatic at diagnosis, presenting with a persistent unexplained leukocytosis (or thrombocytosis) on a routine laboratory test. The most frequent symptoms of CML are related to anaemia and splenomegaly with fatigue, left upper quadrant discomfort and weight loss due to early satiety. Other uncommon signs may include bleeding, thrombosis and leukostasis symptoms.

Once CML is suspected, the diagnosis consists of documenting the presence of the Philadelphia chromosome by karyotype, fluorescent in situ hybridisation (FISH) or polymerase chain reaction (PCR) either on peripheral blood or on bone marrow (BM) aspiration (*Table II*). However, BM aspiration and cytogenetic analysis are mandatory to differentiate CP from AP or BP and to look for additional chromosomal abnormalities. This will influence patient prognosis and management. Baseline PCR should be performed to confirm that the classical fusion gene (p210 e13a2, e14a2 or, less often, the p190e2a2) is detectable by this technique. Because rare transcripts (e13a3, e14a3, e19a2, etc.) are not always searched for or detected by the routinely used PCR techniques, a negative result cannot be used to rule out a diagnosis of CML. Such a rare transcript also precludes the follow-up of the disease by quantitative PCR. In such patients, FISH and karyotype have to be performed to follow the response to TKI.[2,3]

For patients in CP, three scoring systems have been developed to predict disease outcome: Sokal, Euro/Hasford and EUTOS scores (*Table III*). Although Sokal and Euro/Hasford scores have been developed for patients treated with conventional chemotherapy and IFN-α respectively, they also proved useful for predicting the outcome for patients treated with imatinib and were used in studies involving second generation TKIs.[4-7] Since their equation is rather complicated, online calculators are available (http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html). The European Treatment and Outcome Study (EUTOS) score is the only one developed during the imatinib era. It has the advantage of being simple (based solely on the spleen size and the percentage of blood basophils) and it may be superior to the Sokal and Euro/Hasford scores in predicting the achievement of a complete cytogenetic response (CCyR) at eighteen months in patients treated with frontline imatinib.[8] However, it did not predict survival and outcome in an independent cohort of patients.[9] There is no evidence, as yet, that any one of the three risk scores is superior, but the Sokal score is the most widely used.

Table IVa. First and second generation Tyrosine Kinase Inhibitors characteristics. (www.ema.europa.eu)

	Imatinib (Glivec®)	Nilotinib (Tasigna®)	Dasatinib (Sprycel®)
Dosing CP AP BP	 400 mg 1x/d 400 mg 2x/d 400 mg 2x/d	 300 mg 2x/d in 1st line 400 mg 2x/d in 2nd line after failure 400 mg 2x/d 400 mg 2x/d	 100 mg 1x/d 140 mg 1x/d 140 mg 1x/d
Administration	Once daily with a meal and a large glass of water.	12 hours apart. On empty stomach, at least 2h before and 1h after food.	Once daily without regard to food.
Pharmacokinetic properties	Metabolism mainly hepatic ; Minimal renal excretion (13%)	Metabolism mainly hepatic; No renal excretion	Metabolism mainly hepatic ; Minimal renal excretion (4%)
Dose adjustment for liver dysfunction	Use with caution. Maximum recommended dose of 400 mg/d as starting dose. Reduce dose if not tolerated.	Adjustment may not be required however use with caution. ALT or AST > 2.5xULN or total bilirubin > 1.5xULN were excluded from clinical trials.	Adjustment may not be required however use with caution. ALT or AST > 2.5xULN or total bilirubin > 2xULN were excluded from clinical trials.
Dose adjustment for renal dysfunction	Renal dysfunction or on dialysis: use with caution. Maximum recommended dose of 400 mg/d as starting dose. Reduce dose if not tolerated. If tolerated, increase dose for lack of efficacy.	Not studied in patients with serum creatinine > 1.5x ULN. Adjustments may not be necessary.	Not studied in patients with serum creatinine > 3x ULN. Adjustments may not be necessary.
Monitoring CBC Electrolyte Liver Tests Renal function	After 1 week, then 1x/2 weeks for the 1st 3 months, then at each BCR-ABL1 PCR testing (see *Table Xa*)		
Monitoring Other tests	Weight and fluid status.	Lipid profile, Glycaemia; Pancreatic function tests; EKG (D+1 and D+8 after initiation or dosage adjustment) ; TSH (1x/month for 4 months, then every 3 months).	Weight and fluid status; Chest x-ray if suspicion of pleural effusion; EKG if at risk of QT prolongation (arrhythmia, antiarrhythmic medications,…).

First-line treatment

While waiting for the results of the molecular (PCR BCR-ABL1) and cytogenetic (Philadelphia chromosome) testing, hydroxyurea can be initiated if white blood cell (WBC) count is elevated (e.g. >80-100 x 10^9/L), if platelet count is elevated (e.g. >1000 x 10^9/L) or if symptoms of hyperviscosity are present. In this setting, allopurinol can be prescribed to prevent tumour lysis syndrome. Once the diagnosis is confirmed, a TKI can be started. It is not necessary to bring the WBC level to normal with hydroxyurea before starting a TKI. Currently, three TKIs are commonly prescribed for the first line treatment of CML: the first generation TKI, imatinib, and the second generation TKIs, nilotinib and dasatinib (*Table IVa*).

They share common characteristics:

– TKIs are metabolised by the CYP3A4 system and can inhibit other cytochrome P450 pathways. As such, they have many drug interactions (*Tables V, Va and Vb*) and a careful examination of the patient's medication list is essential.

– TKIs are usually well tolerated but numerous adverse events (AEs) have been observed. They vary from one

Table IVb. New Tyrosine Kinase Inhibitors characteristics. (www.ema.europa.eu)

	Bosutinib (Bosulif®)	Ponatinib (Iclusig®)
Dosing CP – AP – BP	500 mg 1x/d	Dose to be redefined to minimize cardiovascular risk. Possibly 30 mg/day, to be decreased to 15 mg/d when patient with MMR
Administration	Once daily with food.	Once daily without regard to food.
Dose adjustment for liver dysfunction	Child A-B-C : 200 mg QD	Not studied. Metabolism mainly hepatic. Use with caution.
Dose adjustment for renal dysfunction	Creatinine > 1.5xUNL were excluded from CML studies.	Not studied. Minimal renal excretion. Adjustment may not be necessary if creatinine clearance ≥ 50 mL/min. Use with caution if creatinine clearance < 50mL/min.
Monitoring CBC Electrolyte Liver Function Tests	1x/2 weeks for the 1st 2 months, then 1x/3 months	
Other tests	Renal function ; Weight and fluid status. Diarrhoea	Baseline EKG ; Glycaemia ; Lipase ; Uric acid ; Weight and fluid status ; Blood pressure; cardiac function; Haemorrhage; signs of thromboembolism; gastro-intestinal perforation.
Drug Interactions CYP3A4 Inducers and Inhibitors **[cf. List]**	Avoid concomitant use.	Avoid concomitant use.
Drugs for gastric acidity	Antacids, H2-antagonists: separate administration by several hours. PPI: Avoid.	Antacids, PPI: avoid, may decrease Ponatinib serum concentration.
Cardiac Drugs	Avoid QT prolonging agents **[cf.list]**	Serious heart failure and arrhythmias were reported with Ponatinib. Monitor for signs of heart failure and arrhythmias.
Anticoagulants		Vitamin K antagonists: Monitor INR closely.
Particular AE	Gastro-intestinal: diarrhoea, nausea, vomiting	Cardiovascular: Hypertension, arterial thrombotic events, stroke. Skin: Dry skin, rash
Cautious use for certain comorbidities	Long QT syndrome	Cardiovascular risk factors Ischemic cardiac disease Hypertension

drug to another but many side effects are common, at different frequencies, to all TKIs. These include myelosuppression, fatigue, fluid retention, gastrointestinal disturbances, hepatotoxicity, pancreatic toxicity, musculoskeletal complaints, skin rash, cardiac toxicities and electrolyte imbalances. These AEs may jeopardise patient compliance and their efficient management is crucial for patient outcome (*Table VI*).

Current guidelines approve all three TKIs as possible choices for the initial management of CP-CML but it is very difficult to decide which TKI is the best for front-line therapy since their respective pros and cons are rather balanced (*Table VII*). The choice of first-line therapy may depend on risk score, priority for a deep response to allow a treatment-free remission protocol, age, presence of comorbid conditions (*Table VIII*), side effect profile, drug interactions, compliance concerns and price. Results obtained with first line TKIs are summarised in *Table IX*. ENESTnd and DASISION are different trials and their results cannot be directly compared.[6,7] While a second generation TKI gives faster and deeper molecular response, it should be noted that

Table V. Drug interactions.*[30] (www.fda.gov)

Drug interactions	Imatinib	Nilotinib	Dasatinib
CYP3A4 Strong Inducers (may decrease TKI plasma levels) **[cf. List]**	Avoid. If cannot be avoided, increase Imatinib dose by at least 50% with careful monitoring. Consider Imatinib plasma level dosage.	Avoid An increased dose of Nilotinib is not likely to compensate for decreased exposure.	Avoid. If required, consider increasing the Dasatinib dose with careful monitoring.
CYP3A4 Strong Inhibitors (may increase TKI plasma levels) **[cf. List]**	Avoid If required, consider Imatinib dose reduction (no formal recommendations) Consider Imatinib plasma level dosage (no formal recommendation)	Avoid. If required: Consider reducing Nilotinib to 200 mg/d (CP) or 300 mg/d (AP) with careful monitoring of the QT interval. When the strong inhibitor is discontinued, allow a wash out period (1 week) prior to adjusting Nilotinib dose upward. If not tolerated, discontinue CYP3A4 inhibitor or withhold Nilotinib temporarily.	Avoid. If required: Consider reducing Dasatinib to 20 mg/d (CP) or 40 mg/d (AP). When the strong inhibitor is discontinued, allow a wash out period (1 week) prior to adjusting Dasatinib dose upward. If not tolerated, discontinue CYP3A4 inhibitor or withhold Dasatinib temporarily.
Drugs for gastric acidity	PPI : ↑ Imatinib exposure	PPI: ↓ Nilotinib absorption → Avoid Antacids, H2-antagonists: separate administration by several hours.	H2-antagonists and PPI: ↓ Dasatinib absorption → Avoid. Antacids: separate administration by several hours.
Cardiac Drugs	Calcium channel blockers (CCB): ↑ CCB exposure. Digoxin: ↓ digoxin absorption	Avoid QT prolonging agents **[cf.list]** ↑ CCB exposure.	Avoid QT Prolonging agents **[cf.list]** ↑ CCB exposure.
Anticoagulants Antiplatelet drugs NSAIDs	Vitamin K antagonists: control INR during the first weeks following initiation of Imatinib NSAIDs: ↑ NSAIDs exposure.	Vitamin K antagonists: control INR during the first weeks following initiation of Nilotinib. NSAIDs: ↑ NSAIDs exposure.	Antiplatelet effect of Dasatinib: Enhanced risk of bleeding, use with caution.

**Word of warning: Non-exhaustive list of drug-interactions. Please check before prescribing.*

long-term survival benefit advantage with second generation TKIs used in first line has not been established.

Detection and management of first-line failure

Once a TKI is initiated, the response must be closely monitored in order to identify patients with an inadequate response to therapy and who require a change in treatment, which will occur in about one third of them.[5] The European LeukemiaNet has published definitions (*Table X*) and monitoring guidelines for first (*Table XI*) and second line treatment (*Table XII*).[2] We recommend to perform BM aspirate and karyotype at three months, and to repeat this procedure at six and twelve months if the patient is not in CCyR. In case of CCyR, patients can be followed only by PCR on blood samples if the classical transcript was detectable at diagnosis. Optimal response is associated with the best long-term outcome, indicating that there is no indication for a change of treatment. Failure means that the patient should receive a different treatment, to limit the risk of progression and death. Warning implies that the characteristics of the disease and the response to treatment require more frequent monitoring, to allow for timely changes in therapy, in case of treatment failure. In case of intolerance to the first line therapy without failure, the treatment should be switched to another TKI approved in first line (imatinib, dasatinib or nilotinib).

In case of warning or failure, treatment incompliance and drug–drug interactions should be ruled out before defining a patient as having a drug-resistance. Then,

Table Va. List of CYP3A4 inducers and inhibitors.*[31]
(www.lexi.com; www.uptodate.com, adapted to the Belgian situation)

Strong Inducers	Moderate Inducers	Strong Inhibitors	Moderate Inhibitors
Carbamazepine	Aprepitant	Atazanavir	Abiraterone
Dexamethasone	Artemether	Boceprevir	Amiodarone
Enzalutamide	Bexarotene	Chloramphenicol	Aprepitant
Mitotane	Bosentan	Clarithromycin	Bicalutamide
Nevirapine	Calcitriol	Cobicistat	Cimetidine
Oxcarbazepine	Clobazam	Darunavir	Ciprofloxacin
Pentobarbital	Dabrafenib	Delavirdine	Clotrimazole
Phenytoin	Deferasirox	Fosamprenavir	Crizotinib
Primidone	Efavirenz	Grapefruit	Cyclosporine
Rifabutin	Etravirine	Indinavir	Danazol
Rifampicin	Felbamate	Itraconazole	Dasatinib
Rifapentine	Flucloxacillin	Ketokonazole	Diltiazem
Rifampicin	Fosaprepitant	Lopinavir	Efavirenz
Rifapentine	Hydrocortisone	Nelfinavir	Erythromycin
St John's wort	Modafinil	Nicardipine	Fluconazole
	Nafcillin	Posaconazole	Fosaprepitant
	Paclitaxel	Ritonavir	Imatinib
	Topiramate	Saquinavir	Metronidazole
	Trametinib	Telaprevir	Miconazole
	Vemurafenib	Telithromycin	Norfloxacin
		Voriconazole	Tetracycline
			Verapamil

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BCR-ABL1 mutational analysis should be performed before changing to other TKIs. Indeed, one of the most common mechanisms of drug resistance involves point mutations in the kinase domain of BCR-ABL1, which impairs the activity of the available TKIs. Most of the mutations that confer resistance to imatinib can be overcome by nilotinib and dasatinib except the T315I mutation which mandates a rapid switch of therapy to allogeneic stem cell transplantation or ponatinib, a third generation TKI active against this mutant.[10] The attitude to adopt when a patient fails to achieve a ≤10% BCR-ABL/ABL PCR at three months is a matter of debate. These patients have a shorter progression-free and overall survival, but the benefit of changing therapy at this time point is not demonstrated.[11] For the ELN, it represents a warning and requires a close follow-up, without an immediate change in therapy.[2] The National Comprehensive Cancer Network (NCCN) guidelines

Table Vb. QT prolonging drugs.* (www.cbip.be)

	Generic Names	Brand Names
Antiarrhythmics	Disopyramide Quinidine Amiodarone Sotalol Flecainide	Rythmodan® - (not available in Belgium) Cordarone® Sotalex® Tambocor®, Apocard®
Antiemetics	Domperidone (caution when > 30 mg/d) Ondansetron (mainly I.V., max. 16 mg/dose)	Motilium® Zofran®
Analgesic	Methadone	Mephenon®
Antipsychotics	Droperidol Pimozide Sertindol Haloperidol	Dehydrobenzperidol® Orap® Serdolect® Haldol®
Antidepressants	Tricyclic antidepressants (mainly in case of overdose) Citalopram Escitalopram	Cipramil® Sipralexa®
CNS stimulant	Atomoxetine	Strattera®
Antimicrobials	Erythromycine (mainly I.V.) Clarithromycine Telithromycine / Azithromycine Moxifloxacine / Levofloxacine / Ofloxacine Amphotericine B Chloroquine Artéméther + Luméfantrine Arténimol + Pipéraquine Pentamidine Atazanavir / Lopinavir / Saquinavir	Erythrocine® Biclar®, Heliclar®, Maclar®, Monoclarium® Ketek® / Zitromax® Avelox®, Proflox® / Tavanic® / Tarivid® Abelcet®, Ambisome® Nivaquine® Riamet® Eurartesim® Pentacarinat® Reyataz® / Kaletra® / Invirase®
Anti-tumour agents	Toremifene Trioxyde d'arsenic TKIs : Bosutinib / Dasatinib / Géfitinib / Imatinib / Lapatinib / Nilotinib / Pazopanib / Sorafénib / Sunitinib	- (not available in Belgium) Trisenox® TKIs: Bosulif® / Sprycel® / Iressa® / Glivec® / Tyverb® / Tasigna® / Votrient® / Nexavar® / Sutent®

**Word of warning: Non-exhaustive list of drug-interactions. Please check before prescribing.*

recommend switching to an alternate TKI other than imatinib if compliance or drug interaction is not an issue.

In case of failure in a patient treated with imatinib, treatment should be switched to one of the second generation TKIs, nilotinib or dasatinib. Bosutinib should be considered for patients in failure to first line treatment when dasatinib or nilotinib are not an option (reimbursed in this indication after approval by the College of Physicians). Since the three medications have not been compared directly in a randomised trial, the choice depends on the presence of specific mutations (*Table XIII*) and patient characteristics. The results of studies with second generation TKIs after imatinib failure are reported in *Table XIV*. Because the studies are different, the results are illustrative and cannot be compared to one another.

For patients receiving a second generation TKI as front-line therapy, definitions of optimal response, warning and failure are similar to imatinib (*Table XI*). In case of failure the treatment should be switched to the other second generation TKI (nilotinib or dasatinib), to bosutinib or to ponatinib (*Table IVb*).

Table VI. Management of TKI adverse events.[3,32]

Adverse event	Management
Nausea	Imatinib and Dasatinib : take medication with a meal and large glass of water Nilotinib : antiemetic if necessary, avoid domperidone
Diarrhoea	Loperamide
Abdominal Pain	Antacids, H2-antagonists : separate administration by several hours Proton Pump Inhibitors : avoid
Fluid retention (Imatinib and Dasatinib) Peripheral oedema	Diuretics, salt restriction.
Periorbital oedema	Steroid-containing cream.
Pleural or cardiac effusion	Observation if minimal. Withhold and reinitiate at decreased dose when effusion resolves. Consider prednisone 20 mg/d for 3 days and diuretics. Thoracocentesis if not resolving or large and symptomatic.
Pulmonary hypertension (Dasatinib)	Permanent discontinuation/switch.
Cardiovascular complications	Careful examination of the possible causality of the TKI, particularly for Ponatinib and Nilotinib. Pros and cons of continuing/switching therapy.
Skin rash	Topical steroids (clobetasol, betamethasone, diflucortolone), occasionally systemic steroids, antihistamines, minimize sun exposure. If severe: dose reduction, interruption or discontinuation.
Musculoskeletal complaints Pain, myalgia, arthralgia	Usually mild to moderate, decrease after a few months. NSAID if not contraindicated. NSAID should be used with caution in Dasatinib treated patients because of the risk of bleeding.
Muscle cramps	Calcium supplement, electrolyte replacement if needed (e.g., magnesium, potassium), tonic water, quinine sulphate.
Hyperglycemia (Nilotinib)	Usually mild, transient and manageable. If grade ≥ 3, restart therapy when recovered to grade 1 with reduced dose. Adjustment of the antidiabetic treatment.
Hepatic Toxicities	Monitor if grade 1 or 2. Interrupt therapy if grade 3; restart a lower dose when recovered to grade 1. Evaluate for other hepatotoxic drugs that may be contributing to toxicity. Permanent discontinuation/switch if severe.
Pancreatic Toxicities (Nilotinib)	Lipase or amylase > 2 x ULN : withhold until ≤ 1.5 x ULN then switch or resume Nilotinib at 300 or 400 mg 1x/d. Permanent discontinuation/switch in case of pancreatitis.
Hematologic toxicities	ANC < 1000/mL or platelets < 50 x 10^9/L : withhold. If ANC > 1000/mL and platelets > 50 x 10^9/L within 2 weeks: resume at prior dose. If ANC < 1000/mL or platelets < 50 x 10^9/L for > 2 weeks, resume at lower dose. Consider filgrastim if recurrent/persistent or sepsis. For grade 3/4 anaemia, CMS and FDA do not support the use of erythropoiesis-stimulating agents.
QT prolongation (Nilotinib, Dasatinib)	QT prolongation > 480 msec: withhold, correct potassium and magnesium levels, review current medications. If QT < 450 msec within 2 weeks : resume at prior dose. If QT 450-480 msec after 2 weeks : resume at lower dose. If QT > 480 msec after dosage reduction : stop treatment.

Table VII. Pros and Cons of each TKI in the first line setting.

	Imatinib		Nilotinib		Dasatinib	
	Pros	**Cons**	**Pros**	**Cons**	**Pros**	**Cons**
Posology	Once daily with food			Every 12h, must fast 2h before and 1h after	Once daily without regard to food	
Response			Less progression to AP – BP compared to Imatinib (≈ 1% vs ≈ 4%) Deeper molecular response but same 3-yr survival		Less progression to AP – BP compared to Imatinib (≈ 2% vs ≈ 5%) Deeper molecular response but same 3-yr survival	
Side effects	Well known side-effect profile	More low grade AEs such as nausea, myalgia, arthralgia and fluid retention. Cases of cardiotoxicity.	Less low grade AE than Imatinib	Skin rash, hyperglycemia, hypertriglyceridemia, QT prolongation, cases of peripheral arterial occlusion (1.4% in ENESTnd after 4 years FU)[33]	Less low grade AEs than Imatinib	Pleural effusion, cases of pulmonary artery hypertension
Price & Availibility	2491€/month. Available in community pharmacy. Authorisation of health insurance medical adviser necessary.			2771€/month. Available in hospital pharmacy only. No authorisation required – justification send to the hospital pharmacy.		3989€/month (3867€/month as of April 1st 2015). Product under contract. Public price does not reflect the acutal cost to the government. Available in hospital pharmacy only. Prior notification of the College of Physicians is required.

Patients presenting the T315I mutation are resistant to all first and second generation TKIs. Therefore once the mutation is detected, these treatments should be stopped. Ponatinib, a third generation TKI, is active against this mutant and is recognised by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in this indication. It is available in Belgium as a medical need program. Ponatinib is also active, to a lesser extent, in patients resistant to first and second generation TKIs without a T315I mutation.[10] However, its use is hampered by the occurrence of frequent cardiovascular problems. In the PACE trial, these included 11.8% of serious arterial thrombotic events after 24-month follow-up: hypertension, myocardial infraction, stroke, peripheral arterial disease and veno-occlusive disease.[12] Therefore ponatinib should be reserved for patients with no alternative and should be used with caution, especially in patients with cardiovascular risk factors. The initial dose of ponatinib, which was 45 mg in the PACE trial, is probably too high and still needs to be determined.[13]

The optimal response to second line therapy is also defined by the ELN (*Table XII*). In case of failure in this setting, ponatinib or bosutinib should be prescribed, and the search for a potential donor should be started if the patient is eligible for allogeneic hematopoietic stem cell transplantation (HSCT).

Treatment discontinuation

TKI therapy is currently considered a life-long treatment but several issues should be considered:

– Chronic low grade side effects that adversely affects the quality of life and may decrease treatment adherence over time

Table VIII. Cautious use of TKIs for certain comorbidities.

	Imatinib	Nilotinib	Dasatinib
Cardio-vascular diseases	Cardiac dysfunction	Ischemic cardiac disease Long QT syndrome Peripheral arterial disease	Ischemic cardiac disease Long QT syndrome Pulmonary hypertension
Pulmonary diseases			Pleural effusion Poor pulmonary function
Liver disease	Hepatic impairment	Hepatic impairment	Hepatic impairment
Gastrointestinal diseases		Pancreatitis Total gastrectomy Lactose intolerance	Lactose intolerance
Endocrinopathies		Diabetes Dyslipidemia	
Renal diseases	Renal failure	Not studied in renal failure	Not studied in renal failure

Table IX. Results of studies comparing Imatinib first line to Nilotinib or Dasatinib (ENESTnd and Dasision are different studies, results can not be directly compared between the two studies).

CML – CP – 1st line treatment	ENESTnd[6]		Dasision[7]	
	Imatinib 400 QD	**Nilotinib 300 BD**	**Imatinib 400 QD**	**Dasatinib 100 QD**
CCyR 1y	65%	80%	72%	83%
MMR 1y	27%	50%	23%	46%
MR4.5 4y[33,34]	23%	40%	30%	37%
OS 4y[33,34]	93.3%	94.3%	92%	93%

– Long term safety of TKIs
– TKIs in women with child bearing potential
– Health care cost

In the Stop Imatinib (STIM) trial, 100 patients with documented CMR (defined as ≥5-log reduction in BCR-ABL1/ABL levels and undetectable BCR-ABL1 transcripts) for more than two years stopped imatinib and were followed closely for molecular relapse. At 36 months, 39% of the patients remained treatment-free without any molecular recurrence. Relapse occurred mainly during the first six months but late relapses have also been observed. Patients with a low Sokal score at diagnosis and imatinib treatment of at least five years have a higher probability to remain treatment-free. Fortunately, patients who experienced a molecular relapse retain sensitivity to imatinib.[14] Discontinuation of second generation TKIs following imatinib failure has also been tested in patients with sustained stable undetectable BCR-ABL1 transcripts but it has been reported in only a small number of patients.[15] Therefore stopping TKI therapy is feasible in selected patients but it should only be done in the context of a clinical trial. It should be noted that when TKI treatment is stopped, BCR-ABL1 transcript must be monitored once per month during the first six to twelve months but INAMI/RIZIV reimburse only four analyses per year.

Table Xa. Cytogenetic and molecular monitoring of CML.[2]

	Source of sample	Type of Assessment	Comments
Karyotype	Bone marrow	Cytogenetic response	At least 20 metaphases to be analysed
FISH	Blood or bone marrow	Complete cytogenetic response defined as < 1% BCR-ABL1 + nuclei of at least 200 nuclei	Useful at diagnosis if karyotype is not interpretable – Only to monitor persistence of CCyR if PCR not available or negative at diagnosis (rare transcripts)
Quantitative RT PCR	Blood	Molecular response	To be analysed in a standardised laboratory (EUTOS) and reported according to the International Scale (IS) as the ratio of BCR-ABL1 transcripts to ABL1 transcripts, or other internationally recognised control transcripts, and it is expressed and reported as BCR-ABL1 %.
Sequencing	Blood or bone marrow	BCR-ABL1 kinase domain mutations	In case of treatment failure or of progression to AP or BP, always required before changing to other TKIs or other therapies.

Accelerated Phase (AP)

Many definitions have been applied to AP-CML (*Table I*). Both the World Health Organization (WHO) and the ELN criteria are frequently used.

Newly diagnosed AP-CML patients are to be considered as high risk CP patients. Only imatinib is approved by the EMA and is reimbursed in Belgium for first line treatment. The maximal dose (up to 400 mg BID) should be prescribed if tolerated. A retrospective study showed that in patients treated with first line imatinib, the CCyR rate was 60% and the two year overall survival 87,8%. Intuitively, more potent second generation inhibitors (nilotinib or dasatinib) should be the first choice in these patients, which is not evidence-based due to the lack of data in this infrequent patient population.[16]

Response should be based on the ELN criteria for CP patients. In patients with an optimal response, TKIs may be continued indefinitely. Treatment discontinuation is not advised for these patients. For patients with warning or failure, the therapy should be switched to a second or third generation TKI and alloSCT is recommended for eligible patients.

In TKI pretreated patients in progression to AP-CML, BCR-ABL1 kinase mutation analysis must be sought and, for allogeneic HSCT-eligible patients, a donor search should be initiated. Treatment should be changed to another TKI (dasatinib 140 mg once daily / nilotinib 400 mg twice daily / ponatinib 45 mg daily if T315I mutation) based upon treatment history and/or BCR-ABL1 mutational analysis and/or comorbidities. Allogeneic HSCT should be considered for all eligible patients. The optimal timing for transplantation is as soon as possible because the disease phase at the time of transplantation is an important prognostic factor for survival. HSCT-eligible patients should thus be transplanted after the best response has been reached.

For HSCT-ineligible patients, TKIs should be continued indefinitely until failure.

Blastic Phase (BP)

According to ELN criteria, BP-CML is defined by the presence of at least 30% blasts in blood or bone marrow or the existence of extramedullary blastic infiltrates, but other definitions have also been proposed (*Table I*).

As for AP-CML, a complete blood count, a bone marrow analysis with cytogenetics and molecular genetics with mutation analysis are needed. Flow cytometry is essential to determine the type of BP: lymphoid-BP, which occurs in ~30% of cases, myeloid-BP in ~50% and the rest being undifferentiated-BP.

Patients who have progressed to BP have a very poor prognosis with median survival ranging between seven and eleven months.[17] Thus allogeneic HSCT represents the only curative option and a donor search should be carried out immediately.

Treatment is based on induction chemotherapy, to control the disease, associated with a TKI followed by allogeneic HSCT as quickly as possible in eligible patients. The type of induction depends on the blast phe-

Table Xb. Definitions of responses and monitoring.[2]

Response	Definitions	Monitoring**
Hematologic- Complete (CHR)	Platelet count < $450x10^9$/L WBC count < 10×10^9/L No immature granulocytes Basophils < 5% Non palpable spleen	Every 15 days until CHR has been confirmed then every 3 months or as required.
Cytogenetic*		
Complete (CCyR)	No Ph+ metaphases	At 3, 6 and every 6 months until a CCyR has been confirmed. Once a CCyR is achieved, FISH on blood cells can be used. If an adequate molecular monitoring can be assured, cytogenetics can be spared after achievement of CCyR. Cytogenetics is required only in case of failure, unexplained cytopenias and if molecular testing is not available.
Partial (PCyR)	1-35% Ph+ metaphases	
Minor	36-65% Ph+ metaphases	
Minimal	66-95% Ph+ metaphases	
None	> 95% Ph+ metaphases	
Molecular		Real Time Quantitative (RT-Q) PCR on the peripheral blood :
Major (MMR or MR 3.0)	Transcript by RT-Q-PCR in blood sample of adequate quality (sensitivity > 10^4) Ratio BCR-ABL1 to ABL1 (or other housekeeping gene) ≤ 0.1% on the international scale (IS)	Every 3 months until MMR has been confirmed then every 3 to 6 months.
MR4.0	(1) detectable disease with < 0.01% BCR-ABL1 IS OR (2) undetectable disease in cDNA with > 10.000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1.	
MR4.5	(1) detectable disease with < 0.0032% BCR-ABL1 IS OR (2) undetectable disease in cDNA with > 32.000 ABL1 transcripts in the same volume of cDNA used to test for BCR-ABL1.	

**Only chromosome banding analysis (CBA) of marrow cell metaphases can be used to assess the degree of CyR, with at least 20 metaphases analysed. FISH of blood interphase cell nuclei could be substituted for CBA of marrow cell metaphases only when a CCyR has been achieved.*

***The response should be assessed with a molecular test (or a cytogenetic test if molecular tests are not available in some countries), but both are recommended whenever possible. Notice that MMR (MR3.0 or better) is optimal for survival, but that a deeper response is likely to be required for a successful discontinuation of treatment. The current price of a chromosome banding analysis (CBA), according to the "Article 33", is around 292 euros (B289) and, nowadays, INAMI/RIZIV reimburses 6 tests per year during the first year, 4 during years 2 to 5 and 1 test per year after the 5th year. The current price of a FISH analysis, according to the "Article 33", is around 182 euros (B180) and, nowadays, INAMI/RIZIV reimburses 6 tests per year during the first year, 4 during years 2 to 5 and 1 test per year after the 5th year. FISH analysis is reimbursed only if CBA is not contributive. The current price of a BCR-ABL1 molecular testing, according to the "Article 33bis" is around 125 euros B3000), and, nowadays, INAMI/RIZIV reimburses 4 tests per year.*

notype. The choice of TKI should be based upon prior therapy and/or BCR-ABL1 mutational testing but also on reimbursement criteria. Therefore, for newly diagnosed BP-CML, only imatinib is available (400 mg BID if tolerated) while for second line treatment dasatinib (140 mg once daily) is accessible. Allo-HSCT without remission or prior return to CP is discouraged but transplantation in aplasia without waiting for marrow recovery may be an option. Considering the limited therapeutic options available, the best management of BP is probably its prevention by an early reduction of BCR-ABL1.

Table XI. Definition of the response to any TKI, first line.[2]
The definitions are the same for patients in CP, AP, and BP, and apply also to 2nd line treatment, when 1st line treatment was changed for intolerance. In case of cytogenetic or molecular data close to the indicated values, a repetition of the tests is recommended.

Time	Optimal	Warnings	Failure
Baseline	NA	High risk scores or CCA/Ph+, "major route" abnormalities*	NA
3 months	Ph+ ≤ 35% and BCR-ABL1 ≤ 10%	Ph+ 36-95% and/or BCR-ABL1 > 10%	No CHR and/or Ph+ > 95%
6 months	Ph+ = 0% and BCR-ABL1 < 1%	Ph+ 1-35% and/or BCR-ABL1 1 – 10%	Ph+ > 35% and/or BCR-ABL1 > 10%
12 months	BCR-ABL1 ≤ 0.1%	BCR-ABL1 0.1 – 1%	Ph+ > 0 % and/or BCR-ABL1 > 1%
Then and at any time	BCR-ABL1 ≤ 0.1%	CCA/Ph- (-7 or 7q-)	Loss of CHR Loss of CCyR Confirmed loss of MMR** Mutations CCA/Ph+

**"Major route" abnormalities includes trisomy 8, trisomy Ph [+der(22)t(9;22)(q34;q11)], isochromosome 17 [i(17)(q10)], trisomy 19, and ider(22)(q10)t(9;22)(q34;q11).*
Note that chromosome 9 deletions and variant translocation at diagnosis have no prognostic value.
***In two consecutive tests, of which one with a BCR-ABL1 transcript levels ≥ 1%.*
NA : Not applicable. CCA/Ph+ : Clonal Chromosome Abnormalities in Ph+ cells ; define an accelerated phase in TKI-naive patients, define a clonal evolution and a therapy failure in TKI-treated patients. CCA/Ph- : Clonal Chromosome Abnormalities in Ph- cells ; no effect on outcome in the absence of dysplasia, with the exception of abnormalities of chromosome 7. MMR = BCR-ABL1 IS ≤ 0.1%.

Table XII. Definition of response for 2nd line treatment, in case of failure of imatinib.[2]
These definitions cannot apply to the evaluation of the response to 3rd line treatment.

Time	Optimal	Warnings	Failure
Baseline	NA	No CHR or Loss of CHR on Imatinib or Lack to CyR to 1st line TKI or High risk	NA
3 months	Ph+ < 65% and/or BCR-ABL1 ≤ 10%	Ph+ 65-95% and/or BCR-ABL1 > 10%	No CHR or Ph+ > 95% or New mutations
6 months	Ph+ < 35% and/or BCR-ABL1 ≤ 10%	Ph+ 35-65%	Ph+ > 65% and/or BCR-ABL1 > 10% and/or New mutations
12 months	Ph+ = 0% and/or BCR-ABL1 ≤ 1%	Ph+ 1-35% and/or BCR-ABL1 1 – 10%	Ph+ > 35 % and/or BCR-ABL1 > 10% and/or New mutations
Then and at any time	BCR-ABL1 ≤ 0.1%	CCA/Ph- (-7 or 7q-) or BCR-ABL1 > 0.1%	Loss of CHR or Loss of CCyR or PCyR or Confirmed loss of MMR* or New mutations or CCA/Ph+

**In two consecutive tests, of which one with a BCR-ABL1 transcript levels ≥ 1%.*

Table XIII. Treatment options based on BCR-ABL1 mutation status.[35] (www.nccn.org/professionals)

Mutations	Treatment options
T315I	Ponatinib, HSCT or clinical trials
V299L	Consider Nilotinib or Ponatinib
T315A	Consider Imatinib, Nilotinib, Bosutinib or Ponatinib
F317L/V/I/C	Consider Nilotinib, Bosutinib or Ponatinib
Y253H, E255K/V,F359V/C/I	Consider Dasatinib, Bosutinib or Ponatinib
Any other mutation	Consider high dose Imatinib, Nilotinib, Dasatinib, Bosutinib or Ponatinib

Table XIV. Response of second or third generation TKI after Imatinib failure.
The data are obtained from different, non-comparative studies. Response rates can therefore not be directly compared between the different drugs.

CML – CP – 2nd line after Imatinib failure	Nilotinib[36] 400 mg BID	Dasatinib[37] 140 mg QD	Bosutinib[38] 500 mg QD	Ponatinib[10] 45 mg QD
Follow up	> 24 months	> 24 months	24 months	17 months
CHR	77%	89%	86%	98%
MCyR	56%	59%	54%	72%
CCyR	41%	44%	41%	63%
OS 2 y	87%	91%	92%	N/A

Pregnancy

The improved outcome of CML has resulted in the necessity of addressing issues relating to fertility and parenting.[18]

For a male patient, there is no formal contraindication for procreating while on imatinib, and the limited data available suggest that in most instances children fathered by such patients have no known abnormalities that can be attributed to imatinib.[19] Concerning dasatinib, very limited data suggest a favourable outcome for babies conceived while their fathers were taking dasatinib.[20] Regarding nilotinib, no published data are available thus far. For the three medications, patients should be advised that the data are still limited. Female patients who wish to conceive are advised to discontinue any TKI during conception and pregnancy. Indeed, although most pregnancies exposed to imatinib have been successful, few of them resulted in serious foetal malformations with an incidence far higher than predicted in the general population.[21] Concerning second generation TKIs, very limited data have described successful pregnancies while exposed to dasatinib or nilotinib.[22-24]

Whenever possible, pregnancies should be planned in order to achieve at least a MMR before treatment interruption. Indeed, when resuming imatinib after discontinuation in pregnancy, an adequate response was only seen in patients who had a MMR before stopping the drug while suboptimal responders either demonstrated the same or a worse response.[25] The risk of this interruption strategy should be clearly explained to the patient. This strategy should only be proposed for patients in CP who have achieved a MMR for at least two years. TKIs should be stopped ideally three months before conception and resumed immediately after delivery. BCR-ABL1 transcripts are monitored every four to six weeks throughout pregnancy (but only four PCR per year are reimbursed by RIZIV/INAMI). In case of

Key messages for clinical practice

1. Diagnosis of chronic myeloid leukaemia requires documentation of the Philadelphia chromosome and a bone marrow aspiration and karyotype for proper classification and prognosis.
2. First line chronic phase patients can be treated with imatinib, nilotinib or dasatinib and have to be monitored according to the 2013 European LeukemiaNet criteria.
3. Adverse events and potential drug interactions have to be carefully monitored during tyrosine kinase inhibitor treatment.
4. Treatment free remission can be an option for patients in deep response, within a clinical trial setting.
5. Nilotinib, dasatinib, bosutinib, ponatinib and allogeneic stem cell transplantations are options for patients resistant or intolerant to their first line tyrosine kinase inhibitor and for advanced phase patients.

progression of the transcript, cytogenetic response should be evaluated. Because of the lack of data and the lack of effectiveness of alternative treatment, timing and type of therapy for a patient progressing during a pregnancy is difficult. IFN is a valid option that can be safely given during pregnancy, but is associated with numerous side effects. In case of excessive WBC, leukapheresis or short pulse hydroxyurea can be used.[3] TKIs should not be used during breast-feeding.

Conclusion

The natural history of CML has dramatically changed since the discovery of TKIs. It has nowadays become a chronic disease manageable with lifelong oral therapy. The main challenge faced by clinicians today is finding the right TKI for the right patient, minimising their side effects, and enhancing patient compliance in order to achieve the best molecular response with the best quality of life. Treatment discontinuation is feasible for a limited number of patients and should be restricted to clinical trials. Several patients may experience treatment failure or disease transformation. In these cases, allogeneic HSCT remains the only curative option.

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