POCKET GUIDELINE

Hematology

Practical management of chronic myeloid leukaemia in Belgium

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A selection of key tables derived from the original paper: " Practical management of chronic myeloid leukaemia in Belgium", written by F.S. Benghiat, Y. Beguin, B. Dessars, T. Devos, P. Lewalle, P. Mineur, N. Straetmans, K. van Eygen, G. Verhoef, and L. Knoops, published in the Belgian Journal of Hematology, volume 6, issue 1, March 2015

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Introduction

Dear Colleagues,

The treatment of patients with chronic myeloid leukemia (CML) is one of the greatest medical success stories of the past 30 years. Today, treatment goals should be to bring our patients life expectancy to normal with minimal impact on their quality of life. To achieve these goals, CML treatment should be individualized with treatment efficiency and side effects carefully monitored. Together with the co-author of this pocket guide, I hope that these practical tables will help you to give the best chances to all CML patients treated in Belgium.

With best wishes,

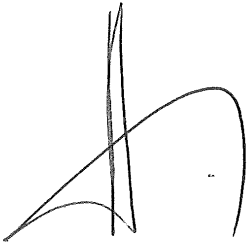

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Table I. Staging of CML according to the ELN or WHO criteria (both can be used).[26,27]

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)

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		
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,…).

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

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.*			

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

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

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.*		

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 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 (ENEST-nd 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%

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) Partial (PCyR) Minor Minimal None	No Ph+ metaphases 1-35% Ph+ metaphases 36-65% Ph+ metaphases 66-95% Ph+ metaphases > 95% 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.
Molecular 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)	Real Time Quantitative (RT-Q) PCR on the peripheral blood: 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.*

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%.*

References

1. Schiffer CA. BCR-ABL tyrosine kinase inhibitors for chronic myelogenous leukemia. N Engl J Med 2007;357:258-65.

2. Baccarani M, Deininger MW, Rosti G, et al. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. Blood 2013;122:872-84.

3. Cortes J, Kantarjian H. How I treat newly diagnosed chronic phase CML.Blood 2012;120:1390-7.

4. Druker BJ, Guilhot F, O'Brien SG, et al. Five-year follow-up of patients receiving imatinib for chronic myeloid leukemia. N Engl J Med 2006;355:2408-17.

5. de Lavallade H, Apperley JF, Khorashad JS, et al. Imatinib for newly diagnosed patients with chronic myeloid leukemia: incidence of sustained responses in an intention-to-treat analysis. J Clin Oncol 2008;26:3358-63.

6. Saglio G, Kim DW, Issaragrisil S, et al. Nilotinib versus imatinib for newly diagnosed chronic myeloid leukemia. N Engl J Med 2010;362:2251-9.

12. Groarke JD, Cheng S, Moslehi J. Cancer-drug discovery and cardiovascular surveillance. N Engl J Med 2013;369:1779-81.

13. Quintas-Cardama A. Ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2014;370:577.

14. Mahon FX, Rea D, Guilhot J, et al. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. Lancet Oncol 2010;11:1029-35.

15. Ross DM, Bartley PA, Goyne J, Morley AA, Seymour JF, Grigg AP. Durable complete molecular remission of chronic myeloid leukemia following dasatinib cessation, despite adverse disease features. Haematologica 2011;96:1720-2.

16. Rea D, Etienne G, Nicolini F, et al. First-line imatinib mesylate in patients with newly diagnosed accelerated phase-chronic myeloid leukemia. Leukemia 2012;26:2254-9.

7. Kantarjian H, Shah NP, Hochhaus A, et al. Dasatinib versus imatinib in newly diagnosed chronic-phase chronic myeloid leukemia. N Engl J Med 2010;362:2260-70.
8. Hasford J, Baccarani M, Hoffmann V, et al. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on imatinib treatment: the EUTOS score. Blood 2011;118:686-92.
9. Jabbour E, Cortes J, Nazha A, et al. EUTOS score is not predictive for survival and outcome in patients with early chronic phase chronic myeloid leukemia treated with tyrosine kinase inhibitors: a single institution experience. Blood 2012;119:4524-6.
10. Cortes JE, Kim DW, Pinilla-Ibarz J, et al. A phase 2 trial of ponatinib in Philadelphia chromosome-positive leukemias. N Engl J Med 2013;369:1783-96.
11. Marin D, Ibrahim AR, Lucas C, et al. Assessment of BCR-ABL1 transcript levels at 3 months is the only requirement for predicting outcome for patients with chronic myeloid leukemia treated with tyrosine kinase inhibitors. J Clin Oncol 2012;30:232-8.
17. Hehlmann R. How I treat CML blast crisis. Blood 2012;120:737-47.
18. Apperley J. Issues of imatinib and pregnancy outcome. J Natl Compr Canc Netw 2009;7:1050-8.
19. Shash E, Bassi S, Cocorocchio E, Colpi GM, Cinieri S, Peccatori FA. Fatherhood during imatinib. Acta Oncol 2011;50:734-5.
20. Oweini H, Otrock ZK, Mahfouz RA, Bazarbachi A. Successful pregnancy involving a man with chronic myeloid leukemia on dasatinib. Arch Gynecol Obstet 2011;283:133-4.
21. Pye SM, Cortes J, Ault P, et al. The effects of imatinib on pregnancy outcome. Blood 2008;111:5505-8.
22. Conchon M, Sanabani SS, Bendit I, Santos FM, Serpa M, Dorliac-Llacer PE. Two successful pregnancies in a woman with chronic myeloid leukemia exposed to nilotinib during the first trimester of her second pregnancy: case study. J Hematol Oncol 2009;2:42.
23. Conchon M, Sanabani SS, Serpa M, et al. Successful Pregnancy and Delivery in a Patient with Chronic Myeloid Leukemia while on Dasatinib Therapy. Adv Hematol 2010;2010:136252.

24. Kroll T, Ames MB, Pruett JA, Fenske TS. Successful management of pregnancy occurring in a patient with chronic myeloid leukemia on dasatinib. Leuk Lymphoma 2010;51:1751-3.

25. Kuwabara A, Babb A, Ibrahim A, et al. Poor outcome after reintroduction of imatinib in patients with chronic myeloid leukemia who interrupt therapy on account of pregnancy without having achieved an optimal response. Blood 2010;116:1014-6.

26. Baccarani M, Saglio G, Goldman J, et al. Evolving concepts in the management of chronic myeloid leukemia: recommendations from an expert panel on behalf of the European LeukemiaNet. Blood 2006;108:1809-20.

27. Vardiman JW, Thiele J, Arber DA, et al. The 2008 revision of the World Health Organization (WHO) classification of myeloid neoplasms and acute leukemia: rationale and important changes. Blood 2009;114:937-51.

28. Sokal JE, Cox EB, Baccarani M, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. Blood 1984;63:789-99.

34. Cortes J, Hochhaus A, Kim DW, et al. Four-Year (Yr) Follow-Up Of Patients (Pts) With Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (CMLCP) Receiving Dasatinib Or Imatinib: Efficacy Based On Early Response. Blood 2013;122:653.

35. Soverini S, Rosti G, Iacobucci I, et al. Choosing the best second-line tyrosine kinase inhibitor in imatinib-resistant chronic myeloid leukemia patients harboring Bcr-Abl kinase domain mutations: how reliable is the inhibitory concentration? Oncologist 2011;16:868-76.

36. Kantarjian HM, Giles FJ, Bhalla KN, et al. Nilotinib is effective in patients with chronic myeloid leukemia in chronic phase after imatinib resistance or intolerance: 24-month follow-up results. Blood 2011;117:1141-5.

37. Shah NP, Kim DW, Kantarjian H, et al. Potent, transient inhibition of BCR-ABL with dasatinib 100 mg daily achieves rapid and durable cytogenetic responses and high transformation-free survival rates in chronic phase chronic myeloid leukemia patients with resistance, suboptimal response or intolerance to imatinib. Haematologica 2010;95:232-40.

29. Hasford J, Pfirrmann M, Hehlmann R, et al. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. J Natl Cancer Inst 1998;90:850-8.
30. Haouala A, Widmer N, Duchosal MA, Montemurro M, Buclin T, Decosterd LA. Drug interactions with the tyrosine kinase inhibitors imatinib, dasatinib, and nilotinib. Blood 2011;117:e75-87.
31. Inhibitors and inducers of CYP enzymes and P-glycoprotein. Med Lett Drugs Ther 2013;55:e44.
32. Deangelo DJ. Managing chronic myeloid leukemia patients intolerant to tyrosine kinase inhibitor therapy. Blood Cancer J 2012;2:e95.
33. Saglio G, Hochhaus A, Hughes T, et al. ENESTnd Update: Nilotinib (NIL) Vs Imatinib (IM) In Patients (pts) With Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (CML-CP) and The Impact Of Early Molecular Response (EMR) and Sokal Risk At Diagnosis On Long-Term Outcomes. Blood 2013;122:92.
38. Cortes JE, Kantarjian HM, Brummendorf TH, et al. Safety and efficacy of bosutinib (SKI-606) in chronic phase Philadelphia chromosome-positive chronic myeloid leukemia patients with resistance or intolerance to imatinib. Blood 2011;118:4567-76.

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