Management and Avoidance of Cardiovascular Adverse Events of TKIs Treatment in CML

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- Each BCR-ABL1–targeted tyrosine kinase inhibitor (TKI) used to treat chronic myeloid leukemia (CML) has a unique toxicity profile that should be considered when assessing the risks and benefits of a TKI
- Potentially severe adverse events have been reported (usually at low frequencies) in patients with CML treated with TKIs: pulmonary arterial hypertension with dasatinib (DAS),[1] arterial occlusive events with nilotinib,[2] and arterial and venous occlusive events with ponatinib[3]

Imatinib Related Adverse Events :

Neutropenia grade ¾	17%	Fluid retention	60%
Anemia grade ¾	4%	Periorbital edema	17%
Thrombocytopenia grade ¾	9%	Rash	9%
Abdominal pain	37%	Diarrhea	45%
Headache	37%	Nausea	50%
Hypertension	4%	Fatigue	39%
Increased serum CRE	8%	Night sweats	15%
Cardiac Failure	1%	Constipation	15%
Muscle cramps	49%	Stomatitis	16%
Musculoskeletal pain	47%	Alopecia	10%
Increased lacrimation	25%	Elevated liver enzymes ¾	5%

Nilotinib Related Adverse Events: (grade ¾)

Anemia	10%
Neutropenia	23%
Thrombocytopenia	28%
Hyperbilirubinemia	7%
Lipase elevation	28% (9%)
Hypophosphatemia	15%
Skin rash	38% (2%)
QT prolongation	1% (> 60 msec)
Diarrhea	14-28% (2%)

Allopecia	11-13%
Increased serum glucose	59% (10%)
Increased serum cholesterol	28%
Peripheral arterial disease	1.9%
CVA	0.8%
IHD	6%
Hypertension	10%
Cardiac arrhythmia	1-3%

Dasatinib Related Adverse Events :

Neutropenia grade ¾	24%	Headache	47%
Anemia grade ¾	12%	Fatigue	37%
Thrombocytopenia grade ¾	23%	Rash	32%
Pleural effusion	25(5.3%)	Diarrhea	41%
Peripheral Edema	10-20%	Nausea	22%
CHF (cardiomyopathy)	2 - 4%	Vomiting	13%
Pericardial effusion	3% (< 1%)	Infection	46% (Gr 3\4 – 6%)
Prolonged QT interval	1%	GI Bleeding	2-9%
PAH	<1%	Hypophosphatemia	9.9%
Musculoskeletal pain	48%	Nodal follicular hyperplasia	2.7%

Ponatinib Related Adverse Events :

Neutropenia grade ¾	24-63%	Headache	25-39%
Anemia grade ¾	9-55%	Fatigue	31%
Thrombocytopenia grade ¾	36-57 %	Rash	34%
Pleural effusion	3-19%	Diarrhea	13-26%
Pericardial effusion	1-3%	Nausea	22%
Hypertension	53-71%	Vomiting	13%
Increased serum AST and ALT	53%	Fever	30%
Increased serum lipase	41%	Constipation	24-47%
Abdominal pain	34-49%		
Increased serum glucose	58%		
Pancreatitis	6%		

Ponatinib Related Adverse Events :

Non –serious and serious arterial and venous adverse events 22% - 45 mg (8% - 15-30 mg)

Cardiovascular events	12% (45 mg)	5% (15-30 mg)
Cerebrovascular events	8% (45 mg)	2% (15-30 mg)
Peripheral vascular events	8% (45 mg)	2% (15-30 mg)
Venous occlusion	2.9%	

Cardiovascular Toxicity:

- QT Interval Prolongation

- Systemic Arterial Hypertension

- Arterial Occlusion
  - IHD
  - ICVE
  - PAOD

- Heart failure

- PAH

QT Interval Prolongation

- All TKIs including Imatinib have the potential to prolog the QT interval

- Clinically symptomatic or asymptomatic but relevant QTc prolongation is uncommon at clinical doses

- Strongly advised to correct any electrolytes imbalance prior to therapy initiation

- Monitor ECG at baseline and during therapy

- Very caution treatment patients with arrhythmogenic risk factors (congenital long QT interval, underlying cardiac disease , QT-interval prolonging medications treatment)

Table 3. Data for QTc prolongation for TKIs

TKI	*Studies*	*Increase of QT interval*	*Result absolute value*	*Conclusion*
Imatinib	ENESTnd imatinib 400 mg ($n=280$)[3]		>480 ms: 0.7% >500 ms: 0.4%	Symptomatic prolongation in 2.5%
Nilotinib	2101 CP and AP[a]	>30 ms: 29.4% >60 ms: 1.3%	>450 ms: 10.2% >480 ms: 1.1% >500 ms: 0.5%	No episode of torsade de pointes
Nilotinib	ENESTnd, nilotinib 300 mg ($n=279$)[3]		>480 or 500 ms: 0%	Symptomatic prolongation in 1.8%
Bosutinib	Healthy adult subjects[73] and BELA trial[74]	No subjects had change from baseline >30 ms	No subjects had QTcB, QTcF, QTcI or QTcN >450 ms.	No clinically relevant PK/PD relationship was observed between bosutinib concentrations and QTc BELA: no data provided
Ponatinib	Phase 1 trial, AP24534-07-101[75]	On 30 mg dosage: decrease of QT On 45 mg dosages: Increase of 3.3 ms		Low risk of QT prolongation
Dasatinib	2440 patients[a,76]	Maximum mean Changes in QTcF (90% upper bound CI) from baseline ranged from 7.0 to 13.4 ms.	>500 ms: 1%	

Abbreviations: AP, accelerated phase; CP, chronic phase. [a]Information taken from investigator brochure.

Congestive Heart Failure

A mechanism for imatinib toxicity on cardiomyocytes initiated by an increased cell death due to activation of the endoplasmic reticulum stress response, collapse of the mitochondrial membrane potential, and release of cytochrome-c with reduction of cellular ATP.

A retrospective review of 1276 p. enrolled in clinical trials, demonstrated 22 (1.7%) p. with CHF, 11 of whom were able to continue treatment with dose adjustments.

Long-term follow up on the IRIS study demonstrated only one patient with left ventricular dysfunction (0.04% per year).

It remains unclear whether cardiac dysfunctions during imatinib treatment were attributable to irreversible myocyte loss or potentially reversible myocyte dysfunction.

Blood. 2007 Aug 15;110(4):1233-7. Epub 2007 Apr 20.

Congestive heart failure is a rare event in patients receiving imatinib therapy.

Atallah E[1], Durand JB, Kantarjian H, Cortes J.

Author information

Abstract

A recent preclinical study suggested that imatinib may be cardiotoxic in some patients. We reviewed all reported serious adverse events of cardiac adverse events occurring in patients on clinical trials involving imatinib. Among 1276 patients enrolled, 22 (1.7%) were identified as having symptoms that could be attributed to systolic heart failure. The median age was 70 years (range, 49 to 83 years). The median time from start of imatinib therapy was 162 days (range, 2-2045 days). At the time these events were reported, 8 (0.6%) were considered possibly or probably related to imatinib. A total of 18 patients had previous medical conditions predisposing to cardiac failure: congestive heart failure (CHF; 6 [27%] patients), diabetes mellitus (6 [27%] patients), hypertension (10 [45%] patients), coronary artery disease (CAD; 8 [36%] patients), arrhythmia (3 [14%] patients), and cardiomyopathy (1 [5%] patient). Of the 22 patients, 11 continued imatinib therapy with dose adjustments and management for the CHF symptoms without further complications. Imatinib therapy as a causal factor of CHF is uncommon, mainly seen in elderly patients with preexisting cardiac conditions. Patients with previous cardiac history should be monitored closely and treated aggressively with standard medical therapy, including diuretics, if they develop symptoms suggestive of heart failure.

PMID: 17449799 DOI: 10.1182/blood-2007-01-070144

Pulmonary arterial hypertension:

PAH and DASATINIB

- Increased mean pulmonary arterial pressure (mPAP) > 25 mmHg at rest.
- Due to vasoconstriction and obstruction of small pulmonary arteries.
- Spontaneous evolution: right heart failure, death.

Dasatinib:

- Precapillary PAH
- Lowest estimate of incidence 0.45%
- Totally or partially reversible upon:
  - Discontinuation of dasatinib
  - Vasoactive drug like Sildenafil
- Risk factors, mechanism: unknown.

Table 1. Vascular AEs recently reported in patients with CML treated with TKIs

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Treatment	*Vascular event*	*IHD*	*ICVE*	*PAOD*
Imatinib	2.1% at 5 years[2]	1.8% in ENESTnd trial 5 years[2] 2% in DASISION trial 5 years[3]	0.4% in ENESTnd trial 5 years[2]	0% in ENESTnd trial 5y[2] 1% in DASISION trial 5 years[3]
Dasatinib	5% at 5 years[3]	4% in DASISION trial 5 years[3]	0.1-1% in Canadian PM[4] 1% of transient ischemic attack in DASISION trial 5 years[3]	0% in DASISION trial 5 years[3]
Nilotinib	7.5% at 5years[2]	3.9% in ENESTnd trial 5 years[2]	1.4% in ENESTnd trial 5 years[2]	2.5% in ENESTnd trial 5 years[2]
Bosutinib	No vascular event described in 10% of cardiac AE at 2 years[4]	no IHD mentioned in 10.2% of cardiac-related AE at 2 years	no ICVE mentioned in 10.2% of cardiac related AE at 2 years[4]	no mentioned in 10.2% of cardiac related AE at 2 years[4]
Ponatinib	7% at 2 years+7% cerebrovascular occlusion+10% cardiovascular occlusion+19% arterial occlusion & thrombosis+7% Peripheral Occlusion 7%[5]	3% at 2 years[5]	3% at 2 years[5]	1% at 2 years[5]

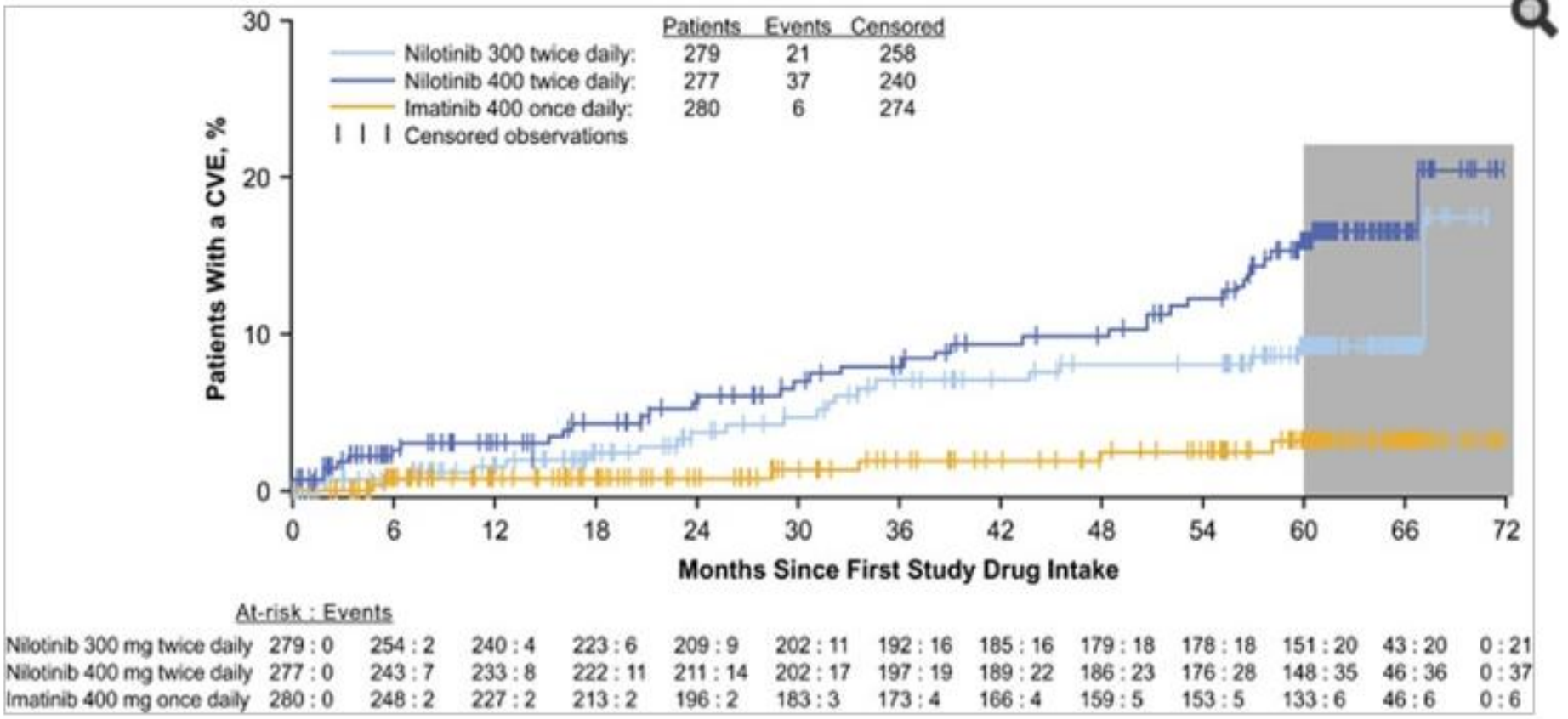
Abbreviations: ICVE, ischemic cerebrovascular event; IHD, ischemic heart disease; PAOD, peripheral arterial occlusive disease; PM, product monograph.

	Nilo 300	Nilo 400	IM
QT prolongation	<3%	<3%	<3%
HTN	10.4%	8.3%	4.3%
Pulm HTN	0%	2%	0%
CVEs	7.5%	13.4%	2.1%

The cumulative frequency of patients with CVEs increased linearly with time on treatment.

Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial

A Hochhaus,[1,*,16] G Saglio,[2,16] T P Hughes,[3] R A Larson,[4] D-W Kim,[5] S Issaragrisil,[6] P D le Coutre,[7] G Etienne,[8] P E Dorlhiac-Llacer,[9] R E Clark,[10] I W Flinn,[11] H Nakamae,[12] B Donohue,[13] W Deng,[13] D Dalal,[13] H D Menssen,[14] and H M Kantarjian[15]



Clinical Risk Factors for Vascular AEs:

- Male
- Age
- History of smoking
- Hypertension
- Coronary heart disease
- Diabetes mellitus
- BMI

Biochemical Risk Factors:

- High cholesterol (LDL)
- Low HDL
- High triglycerides
- High blood glucose and HbA1C

Table 4. Relative Risk of Serious Arterial Occlusive Events by Risk Category (Univariate Analysis)

Risk Category	Rate of Serious AOEs in Patients With Risk Category[a] %	Rate of Serious AOEs in Patients Without Risk Category[b] %	Relative Risk (95% CI)
Age ≥65 years (n=155)	26	14	1.8 (1.2–2.7)
Male (n=238)	22	14	1.5 (1.0–2.3)
History of diabetes[c] (n=72)	32	16	2.0 (1.4–3.1)
History of ischemic heart disease[d] (n=101)	33	14	2.3 (1.6–3.4)
History of hypertension[e] (n=240)	25	10	2.5 (1.6–4.0)
History of hypercholesterolemia[f] (n=228)	24	12	2.0 (1.3–3.0)
History of nonischemic heart disease[d] (n=193)	20	17	1.2 (0.8–1.8)
History of obesity[g] (n=109)	20	18	1.1 (0.7–1.8)

Risk category includes intrinsic factors (age, gender), widely accepted cardiovascular risk factors (diabetes, hypertension, hypercholesterolemia, and obesity), and history of disease

[a] Patients with risk category who had serious AOE divided by total number of patients with risk category

[b] Patients without risk category who had serious AOE divided by total number of patients without risk category

[c] Includes medical history, prior concomitant medication, and/or baseline glucose grade ≥2

[d] Includes medical history and/or prior concomitant medication

[e] Includes medical history, prior concomitant medication, and/or baseline blood pressure grade ≥2

[f] Includes medical history, prior concomitant medication, and/or baseline triglycerides grade ≥1

[g] Includes medical history and/or baseline body mass index ≥30 kg/m^2

Supplemental Table 4. Exploratory analysis of the frequency of cardiovascular events according to Framingham risk category at baseline and treatment arm

	Nilotinib 300 mg twice daily (n = 259)	**Nilotinib 400 mg twice daily (n = 266)**	**Imatinib 400 mg once daily (n = 264)**
Low Framingham Risk Category (< 10%)	**n = 178**	**n = 176**	**n = 182**
Any CVE, n (%)	**3 (1.7)**	**11 (6.3)**	**2 (1.1)**
Ischemic heart disease	3 (1.7)	8 (4.5)	2 (1.1)
Ischemic cerebrovascular event	0	2 (1.1)	0
Peripheral artery disease	0	1 (0.6)	0
Intermediate Framingham Risk Category (≥ 10% to < 20%)	**n = 41**	**n = 52**	**n = 49**
Any CVE, n (%)	**5 (12.2)**	**13 (25.0)**	**2 (4.1)**
Ischemic heart disease	3 (7.3)	8 (15.4)	1 (2.0)
Ischemic cerebrovascular event	1 (2.4)	5 (9.6)	1 (2.0)
Peripheral artery disease	1 (2.4)	1 (1.9)	0
High Framingham Risk Category (≥ 20%)	**n = 40**	**n = 38**	**n = 33**
Any CVE, n (%)	**7 (17.5)**	**9 (23.7)**	**1 (3.0)**
Ischemic heart disease	1 (2.5)	5 (13.2)	1 (3.0)
Ischemic cerebrovascular event	2 (5.0)	1 (2.6)	0
Peripheral artery disease	4 (10.0)	4 (10.5)	0

Abbreviation: CVE, cardiovascular event.

Table 2

Clinical risk factors contributing/predisposing to the occurrence of vascular adverse events (VAE) in CML patients treated with nilotinib or ponatinib.

Specific risk factor that may contribute	
Risk factor type	to VAE development during TKI therapy
Predisposing genetic factors	genetic variations predisposing to the occurrence of hypercholesterolemia or the development of diabetes mellitus
Age and sex[a]	advanced age, males > females
Acquired somatic mutations	clonal age-related hematopoiesis; clonal hematopoiesis of indeterminate potential (may predispose for development of CML as well as development of VAE)
Life-style-related risk factors	nicotine consumption[a], adipositas, refused/irregular drug intake
Pre-existing overt co-morbidities	arterial hypertension[a], atherosclerosis, hypercholesterolemia[a], diabetes mellitus, thrombosis, stroke, other arteriopathies
Dose of TKI and TKI sequence	higher doses of nilotinib (800 mg/day) or ponatinib (45 mg/day); sequential exposure to nilotinib and ponatinib (see also below: time of exposure to TKI).
Time of TKI therapy	longer exposure to nilotinib or ponatinib: most VAE occur after 12 months – and VAE continue to accumulate over time

Abbreviations: VAE, vascular adverse event; TKI, tyrosine kinase inhibitor.

[a] These risk factors are included in the European Society for Cardioloy (ESC) Score.

European LeukemiaNet recommendations for the management and avoidance of adverse events of treatment in chronic myeloid leukaemia

JL Steegmann[1], M Baccarani[2], M Breccia[3], LF Casado[4], V García-Gutiérrez[5], A Hochhaus[6], D-W Kim[7], TD Kim[8], HJ Khoury[9], P Le Coutre[8], J Mayer[10], D Milojkovic[11], K Porkka[12,13], D Rea[14], G Rosti[2], S Saussele[15], R Hehlmann[16] and RE Clark[17]

PAOD:

- Performing the ankle-brachial index or duplex ultrasonography in all newly diagnosed patients aged over 65 years or younger with cardiovascular risk factors, and repeat every 6-12 months

- baseline parameters of fasting glucose , HbA1C, lipids and creatinine, and repeat these parameters every 6-12 months

- In patients with emergent PAOD while on ponatinib or nilotinib, switching to an alternative TKI is recommended

Choice of TKI depending on CV risk factors:

- No absolute contraindication for using any given TKI if comorbidities are considered

- The balance between efficacy and toxicity alters

- In first-line treatment of CP CML in patients at very high risk of CVD, Imatinib or Dasatinib are preferred options

- In low or moderate CV risk patients , any, TKI can be considered

- In all cases, correction of all the cardiovascular risk factors is recommended

Prevention of cardiac problems:

- Baseline and follow - up ECG (Nilotinib – before initiation, then 7 days after start, after dose increase and periodically)

- The development of arrhythmias should prompt the interruption of the TKI and consultation with a cardiologist

- Arterial hypertension must be actively treated

- Baseline echocardiography (Dasatinib and Ponatinib – every 12 months)

Proposed strategies to minimize the risk of VAE-evolution in patients with CML.

A: Personalized medicine approaches — patient selection:

Selection of patients and selection of TKI based on co-morbidities, cardiovascular risk factors, and the biology of CML
- Exclude patients with cardiovascular co-morbidities from therapy with nilotinib and ponatinib
- Exclude patients with cardiovascular risk factors (high ESC score, molecular risk factors) from therapy with nilotinib and ponatinib

B: During treatment: treatment algorithms, schedules and dosing

Frontline use of imatinib in patients with CP CML
- Keep nilotinib and ponatinib exposure times to a minimum
- Reduce the dose of nilotinib or ponatinib if possible
- Avoid sequential application of nilotinib and ponatinib
- Switch to other TKI with lower risk concerning VAE development once a deep MR has been reached (prophylaxis)
- Switch to other TKI with lower risk concerning VAE development once a VAE has developed

C: Alternative treatment concepts and co-medication

Discontinue TKI therapy after 2 years in deep MR (MR4 or deeper)
- Stem cell transplantation = SCT (young and fit patients)[a]
- Antibody-based CML stem cell eradication followed by TKI discontinuation
- Discontinue TKI therapy and introduce immunotherapy or other experimental therapies as maintenance
- Prophylactic co-medication with aspirin, gliptins, and statins
- TKI rotation therapy: combining more toxic TKI with less toxic TKI

Abbreviation: CP, chronic phase; CML, chronic myeloid leukemia; VAE, vascular adverse event; TKI, tyrosine kinase inhibitor; MR, molecular response; ESC, European Society for Cardiology.

[a] In young and fit patients who are potential candidates for SCT, it is of considerable importance to avoid any occurrence of a VAE before SCT. Therefore, in these patients, it is as important to select optimal and safe therapy as in older patients with comorbidities.