Vascular toxicity of nilotinib in chronic myeloid leukemia (CML) : literature review

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Introduction :

CML is a myeloproliferative syndrome whose treatment was revolutionized by the advent of tyrosine kinase inhibitors (TKI).
The first generation released in 2001 was imatinib.
In response to resistance to this treatment, nilotinib, 2nd generationTKI was developed.
Initially unknown, its vascular adverse events are now reported in the literature, including lower extremity artery disease (LEAD), ischemic heart disease and ischemic neurovascular events (constituted stroke and transient ischemic attack (TIA)).

The aim of this work was to conduct a literature review from 2011 to 2018 on the prevalence of cardiovascular effects of nilotinib and the presence or absence of predisposing factors.

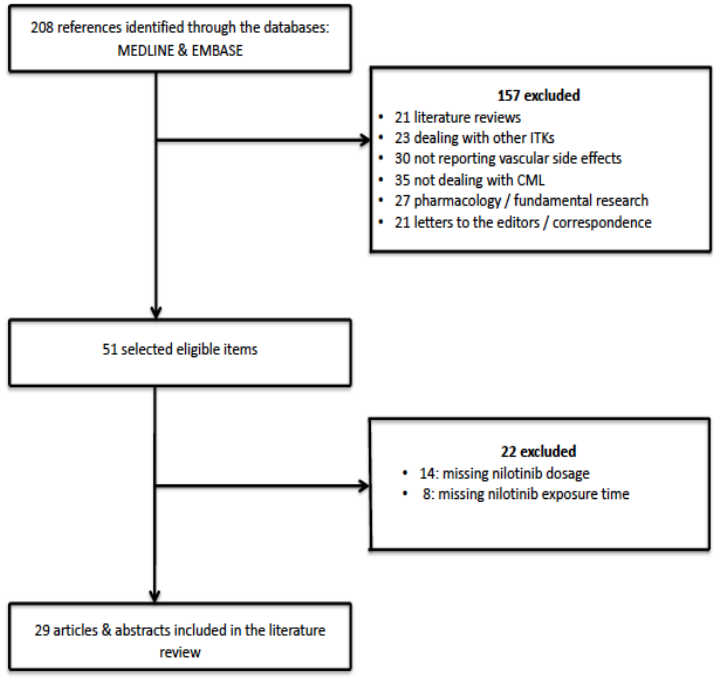
Methods :

MEDLINE :

« Leukemia, Myelogenous, Chronic, BCR-ABL Positive » AND « 4-methyl-N-(3-(4-methylimidazol-1-yl) -5-(trifluoromethyl)phenyl)-3- ((4-pyridin-3-ylpyrimidin-2-yl) amino)benzamide » AND « Arterial Occlusive Diseases ».

EMBASE :

« nilotinib » {Title/Abstract} AND CML {Title/Abstract} AND « renal artery stenosis » {Title/Abstract} OR « Leukemia, Myelogenous, Chronic, BCR-ABL Positive » AND « 4-methyl-N-(3-(4-methylimidazol-1-yl) -5-(trifluoromethyl)phenyl)-3- ((4-pyridin-3-ylpyrimidin-2-yl)aminobenzamide » AND « Arterial Occlusive Diseases » OR « nilotinib » {Title/Abstract} AND CML {Title/Abstract} AND peripheral artery disease {Title/Abstract}.



Results :

Total population n	10334
Patients treated by nilotinib n (%)	6628 (64,1)
CV events n (%)	359 (5,4)
CeVasc events n (%) Stroke TIA Internal carotide stenosis	37 (10,1) 31 (83,8) 1 (2,7) 5 (13,5)
IHD n (%) Stable angina Unstable angina Myocardial infarction Acute Coronary Syndrome	197 (54,9) 2 (1,0) 2 (1,0) 179 (90,9) 14 (7,0)
Sudden death n (%)	2 (0,5)
Aorta stenosis n (%)	1 (0,3)
Renal arteries n (%)	3 (0,8)
LEAD n (%)	112 (31,2)
Digestive arteries n (%)	2 (0,5)
Thrombus n (%)	0 (0)
Pathological ABI n (%)	5 (1,4)
Average duration of nilotinib treatment (months)	29,2
Average follow-up (months)	32,0

Characteristics of patients treated with nilotinib for chronic phase CML

Among patients on nilotinib
5.4% had an adverse cardiovascular event, distributed as follows :

1. Ischemic heart disease (54.9%)
2. LEAD (31.2%)
3. Cerebrovascular ischemia (10.1%)
4. Other territories (3.8%)

Treatment duration: 29.2 months.

←

Nilotinib was prescribed in different doses: 600 or 800 mg per day.
Cardiovascular adverse events were dose-dependent and significantly more frequent below 800mg vs. 600mg per day: 6.8% vs. 4.5%, p= 0.0001, respectively. →

Dose	600 mg/d	800 mg/d	p-value
Total population n (%)	3961 (59,8)	2667 (40,2)	
Total CV events n (%)	178 (4,5)	181 (6,8)	***
CeVasc events n (%) Stroke TIA Internal carotide stenosis	23 (0,6) 22 1 0	14 (0,5) 9 0 5	ns ns ns *
IHD n (%) Stable angina Unstable angina Myocardial infarction Acute Coronary Syndrome	102 (2,6) 0 1 100 1	95 (3,6) 2 1 79 13	* ns ns ns ***
Sudden death n (%)	0 (0)	2 (0,07)	ns
Aorta stenosis n (%)	0 (0)	1 (0,03)	ns
Renal arteries n (%)	0 (0)	3 (0,1)	ns
LEAD n (%)	53 (1,3)	59 (2,2)	**
Digestive arteries n (%)	0 (0)	2 (0,07)	ns
Thrombus n (%)	0 (0)	0 (0)	
Average exposure time (months)	25,9	31,0	
Pathological ABI n (%)	NS	5	

Number of cardiovascular events in patients treated with nilotinib as a function of dose used
* p<0.05 ; ** p<0.01 ; *** p<0.001

Duration of exposure to nilotinib (months)	≤12	12,1-24	24,1-36	36,1-48	≥48	p-value
Patients treated by nilotinib n	370	3089	1451	1592	126	
Total CV events n (%)	23	178	63	89	6	ns
CeVasc events n (%) Stroke TIA Internal carotide stenosis	1 1 0 0	23 22 1 0	7 4 0 3	6 4 0 2	0 0 0 0	ns ns ns ns
IHD n (%) Stable angina Unstable angina Myocardial infarction Acute Coronary Syndrome	11 0 0 11 0	100 0 1 98 1	32 1 1 21 9	52 1 0 47 4	2 0 0 2 0	ns ns ns ** **
Sudden death n (%)	0	0	2	0	0	ns
Aorta stenosis n (%)	0	0	0	1	0	ns
Renal arteries n (%)	1	2	0	0	0	ns
LEAD n (%)	8	52	22	26	4	ns
Digestive arteries n (%)	1	1	0	0	0	ns
Thrombus n (%)	0	0	0	0	0	
Pathological ABI n (%)	1	0	0	4	0	*

Number of cardiovascular events by duration of nilotinib therapy in CML patients * p<0.05 ; ** p<0.01 ; *** p<0.001

Myocardial infarction is more frequent between 12 and 24 months of treatment (p=0.009). But the risk of ischemic heart disease persists all the time of exposure

	Nilotinib	Imatinib	p-value
Patients, n	2955	2627	
Total CV events, n (%)	124 (4,2)	22 (0,8)	***
CeVasc events, n (%)	9 (0,3)	1 (0,04)	*
IHD n (%)	81 (2,7)	19 (0,7)	***
LEAD n (%)	34 (1,2)	2 (0,08)	***

Number of cardiovascular events occurring in patients treated with nilotnib versus imatinib
* p<0.05 ; ** p<0.01 ; *** p<0.001

Comparison of the occurrence of cardiovascular side events according to the ITK used.
Total cardiovascular events are significantly higher in patients treated with nilotinib than imatinib (1st generation ITK).

Conclusion :

- **Cardiovascular side effects were more frequent in patients taking nilotinib than imatinib.**
- **In the favoring factors were a dose effect, and a duration of exposure effect.**
- **The overall cardiovascular assessment of the patient with CML is important in the choice of TKI and its cardiovascular prognosis.**