Atherothrombotic adverse effects of tyrosine kinase inhibitors in patients with chronic myeloid leukemia

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INTRODUCTION

Tyrosine kinase inhibitors (TKI) have significantly improved the prognosis of patients with chronic myeloid leukemia (CML); however, their use is associated with a risk of atherothrombotic adverse effects (ATAE).

AIM

To determine the incidence, profile, and risk factors of ATAE in patients with CML receiving TKI, taking into account cardiovascular (CV) risk stratification.

METHODS

159 patients with CML were analyzed. The following parameters were assessed:

- demographic characteristics
- risk category according to the HFA-ICOS scale
- CV risk according to the ESC 2021 stratification
- TKI therapy and lipid profile
- vascular remodeling parameters
- incidence of ATAE

Predictors of ATAE and event-free survival (EFS) in patients with different CV risk were identified.

CONCLUSIONS

In patients with CML, ATAE are associated with initially high CV risk.

Nilotinib and ponatinib demonstrated the most unfavorable profiles of toxicity.

These findings highlight the importance of CV risk assessment before initiation of TKI and its dynamic monitoring during treatment.

RESULTS

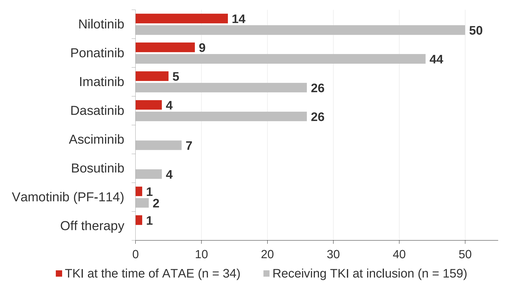
ATAE incidence and profile

ATAE were registered in 34 of 159 patients (21.4%). The median time from initiation of the TKI associated with the development of ATAE to the event was 39.2 months.

Event	n (% of 34 / % of 159)
Stable angina / other stable CAD	**5 (15% / 3%)**
Unstable angina	1 (3% / 0.6%)
Acute myocardial infarction	1 (3% / 0.6%)
Peripheral atherosclerosis, significant *	**5 (15% / 3%)**
Peripheral atherosclerosis, non-significant *	**8 (23% / 5%)**
Visceral artery atherosclerosis	1 (3% / 0.6%)
Stroke or transient ischaemic attack	**7 (20% / 4%)**
Pulmonary embolism	1 (3% / 0.6%)
Sudden cardiac death	1 (3% / 0.6%)
Chronic heart failure	2 (6% / 1%)
Superficial leg vein thrombosis	1 (3% / 0.6%)
Peripheral artery thrombosis	1 (3% / 0.6%)

TKI at the time of ATAE

ATAE developed in 14 of 34 patients (41%) receiving nilotinib and in 9 of 34 (26%) receiving ponatinib (p = 0.05).



ATAE by cardiovascular risk category (n = 34)

Risk score	Low / moderate	High	Very high	p
SCORE2 / SCORE2-OP†	**1 (3%)**	**6 (18%)**	**16 (47%)**	**0.027**
CV risk category, ESC 2021	**5 (14%)**	**6 (18%)**	**23 (68%)**	**0.002**
HFA-ICOS	**9 (27%)**	**20 (59%)**	**5 (14%)**	**0.055**

Predictors of ATAE

Predictor	Univariate p	HR (95% CI)	Multivariable p
Age	0.009	–	–
High / very high CV risk, ESC 2021	0.038	–	–
High / very high risk, HFA-ICOS	**0.007**	**2.22 (1.02–4.79)**	**0.04**
Non-target lipid profile ‡	**0.006**	**3.83 (1.45–10.09)**	**0.026**
Ankle–brachial index < 0.9 ‡	**0.005**	**1.99 (1.29–3.10)**	**0.002**
Carotid intima–media thickness > 0.9 mm ‡	0.047	–	–
Non-significant in univariate analysis: sex, body mass index > 30 kg/m², smoking, diabetes mellitus, arterial hypertension, history of CV disease, > 2 TKI lines before ATAE, exposure to nilotinib, dasatinib or ponatinib	0.111–0.777	–	–

** haemodynamically significant / non-significant peripheral artery atherosclerosis.*

† risk not determined in 11 patients (32%).

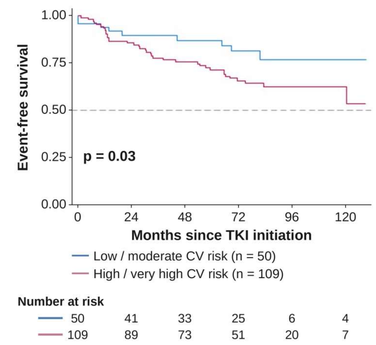
‡ assessed 6–12 months after initiation of the TKI on which ATAE developed.

ATAE – atherothrombotic adverse events; CAD – coronary artery disease; CI – confidence interval; CV – cardiovascular; EFS – event-free survival; ESC – European Society of Cardiology; HR – hazard ratio; TKI – tyrosine kinase inhibitors.

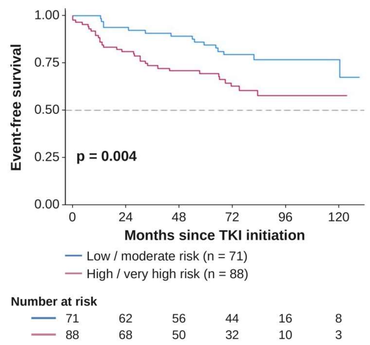
EVENT-FREE SURVIVAL

Five-year EFS in patients at low / moderate versus high / very high CV risk was 93% versus 77% (ESC 2021; p = 0.03) and 90% versus 75% (HFA-ICOS; p = 0.004).

ESC 2021 risk category



HFA-ICOS risk category



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