OPEN ACCESS Freely available online

Journal of Vascular Medicine & Surgery

Commentary

Is Nilotinib Therapy at Risk of Unstable Atheroma?

El Harake Sarah[1], Charbonnier Aude[2], Sarlon-Bartoli Gabrielle[1*]

[1]Department of Vascular Medicine, Aix-Marseille University, Assistance Publique Hôpitaux de Marseille-Hôpital de la Timone, 264, Rue Saint-Pierre, 13385 Marseille Cedex 05, France; [2]Institute Paoli-Calmettes, département d'Onco- hématologie, 232, Boulevard Sainte-Marguerite, BP 156, 13273 Marseille Cedex 9, France

DESCRIPTION

Second and third generation tyrosine kinase inhibitors like nilotinib have been validated in daily practice for the treatment of Chronic Myeloid Leukaemia (CML). We described recently for the first-time the aspect of arterial ultrasound lesion of CML patients during nilotinib therapy [1]. We demonstrated in this short cohort of 74 patients that 33.8% of patients had ultrasound arterial anomalies when they systematically screened by a vascular specialist. This result are in phase of few studies suggested a higher prevalence of Peripheral Arterial Disease (PAD) during this therapy almost 30% [2-8]. Even if no significant vascular adverse events had been reported in initial clinical trials (<1%) [9,10]. In our work the most involved territory was the carotid bulb for 44% of the affected patients like in the Figure 1.

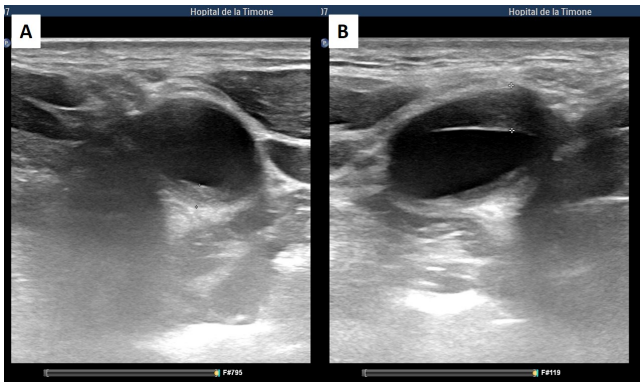

Figure 1: Example of bilateral echolucent carotid plaque. A right carotid bulb; B left carotid bulb. 39 years men without cardiovascular risk factors, CML since 5 years, nilotinib during 4 years, cholesterol LDL 1.5 g/l.

88% of the arterial ultrasound anomalies were plaques, 44%>50% stenosis and 12% occlusion. 72.7% of the plaques were echolucent or hypoechogenic. In fact with ultrasound imaging different atheroma anomalies can be described: plaque and its echogenicity, stenosis or occlusion. The aspect of arterial ultrasound lesion is very important particularly the grayscale (echogenicity). Echolucent or hypoechogenic plaques are associated with unstable atheroma because it reflects lipid core of atheroma with thin fibrous cap [11]. In literature, the carotid plaques with low grayscale median were associated with a twofold increase in stroke [12,13]. These echolucent lesions are sometimes difficult to detect during ultrasonography because echogenicity is similar to the circulating blood. This ultrasound aspect may be secondary to the increase in blood lipids sometimes induced by nilotinib [14]. Also in our study, patients with clinical and/or ultrasound arterial anomalies at baseline were significantly older (64.9 *vs.* 49.3 P<0.001), older at nilotinib initiation (60.8 *vs* 46.5 P<0.001), with more arterial hypertension (40% *vs.* 12.2% P=0.01), with more cardiovascular risk factors (P=0.03). These results are closed from literature that underlying predisposing factors of vascular adverse events with nilotinib therapy: High doses, long exposure to nilotinib and pre-existing cardiovascular risk factors [8,15]. To response at this adverse event in 2016 the France Intergroupe des Leucémies Myeloides Chroniques proposed practical recommendations to minimize the risk and the severity of cardiovascular events in nilotinib-treated patients [16]. Thus a moderate SCORE risk encourages screening arteries including carotid and leg arteries with duplex ultrasound. In these recommendations a low SCORE risk patient should not be systematically detected by ultrasound however in our cohort, in patient with no cardiovascular risk factor, 12.5% had vascular anomalies (n=24). It was closed from others data: Some PAD occurred in younger patients without risks factors [17]. Ultrasonography is a widely painless accessible method to detect arterial anomalies, less expensive than other examinations. In conclusion, treatment with nilotinib seems to be associated to atherosclerosis. The prevalence of ultrasound arterial anomalies is high, especially with longue nilotinib exposure, in older patients and in the presence of several cardiovascular risk factors. Ultrasound characteristics are high frequency of echolucent plaques which reflect unstable atheroma. We believe that the initiation of nilotinib therapy should systematically be associated with a cardiovascular evaluation in all patients, even in the absence of cardiovascular

Correspondence to: Sarlon-Bartoli Gabrielle, Department of Vascular Exploration and Medicine Unit, Aix-Marseille University, Assistance Publique Hôpitaux de Marseille-Hôpital de la Timone, 264, rue Saint-Pierre, France, E-mail: gabrielle.sarlon@ap-hm.fr

Received: September 14, 2021; **Accepted**: September 28, 2021; **Published**: October 05, 2021

Citation: Sarah EH, Aude C, Gabrielle SB (2021) Is Nilotinib Therapy at Risk of Unstable Atheroma? J Vasc Med Surg. 9: 005.

Copyright: © 2021 Sarah EH, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

risk factors. We also believe in the importance of close vascular follow-up in these patients and regular monitoring of the biological lipid profile of these patients.

REFERENCES

1. Sarlon-Bartoli G, Michel Q, Sarlon E, Carcopino-Tusoli M, Suchon P, Soler R, et al. Ultrasound arterial anomalies in patients exposed to nilotinib therapy for chronic myeloid leukemia. J Med Vasc. 2021; 46 (2): 66-71.
2. Aichberger KJ, Herndlhofer S, Schernthaner GH, Schillinger M, Mitterbauer-Hohendanner G, Sillaber C, et al. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in CML. Am J Hematol. 2011; 86 (7): 533-539.
3. Le Coutre P, Rea D, Abruzzese E, Dombret H, Trawinska MM, Herndlhofer S, et al. Severe peripheral arterial disease during nilotinib therapy. J Natl Cancer Inst. 2011; 103 (17): 1347-1348.
4. Kim TD, Rea D, Schwarz M, Grille P, Nicolini FE, Rosti G, et al. Peripheral artery occlusive disease in chronic phase chronic myeloid leukemia patients treated with nilotinib or imatinib. Leukemia. 2013; 27 (6): 1316-1321.
5. Giles FJ, Mauro MJ, Hong F, Ortmann CE, McNeill C, Woodman RC, et al. Rates of peripheral arterial occlusive disease in patients with chronic myeloid leukemia in the chronic phase treated with imatinib, nilotinib, or non-tyrosine kinase therapy: A retrospective cohort analysis. Leukemia. 2013; 27 (6): 1310-1315.
6. Levato L, Cantaffa R, Kropp MG, Magro D, Piro E, Molica S. Progressive peripheral arterial occlusive disease and other vascular events during nilotinib therapy in chronic myeloid leukemia: A single institution study. Eur J Haematol. 2013; 90 (6): 531-532.
7. Mirault T, Rea D, Azarine A, Messas E. Rapid onset of peripheral artery disease in a chronic myeloid leukemia patient without prior arterial disorder: Direct relationship with nilotinib exposure and clinical outcome. Eur J Haematol. 2015; 94 (4): 363-367.
8. Bondon-Guitton E, Combret S, Pérault-Pochat MC, Stève-Dumont M, Bagheri H, Huguet F, et al. Cardiovascular risk profile of patients with peripheral arterial occlusive disease during nilotinib therapy. Target Oncol. 2016; 11 (4): 549-552.
9. Kantarjian HM, Giles FJ, Bhalla KN, Pinilla-Ibarz J, Larson RA, Gattermann N, 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 (4): 1141-1145.
10. Annex I. Summary of product characteristics. EMA. 2014.
11. Stary HC, Chandler AB, Dinsmore RE, Fuster V, Glagov S, Insull Jr W, et al. A definition of advanced types of atherosclerotic lesions and a histological classification of atherosclerosis: A report from the Committee on Vascular Lesions of the Council on Arteriosclerosis. J Am Heart Assoc. 1995; 92 (5): 1355-1374.
12. Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: The Tromsø study. Circulation. 2001; 103 (17): 2171-2175.
13. Gupta A, Kesavabhotla K, Baradaran H, Kamel H, Pandya A, Giambrone AE, et al. Plaque echolucency and stroke risk in asymptomatic carotid stenosis: A systematic review and meta-analysis. Stroke. 2015; 46 (1): 91-97.
14. Rea D, Mirault T, Cluzeau T, Gautier JF, Guilhot F, Dombret H, et al. Early onset hypercholesterolemia induced by the 2nd-generation tyrosine kinase inhibitor nilotinib in patients with chronic phase-chronic myeloid leukemia. Haematologica. 2014; 99 (7): 1197-1203.
15. Hochhaus A, Saglio G, Hughes TP, Larson RA, Kim DW, Issaragrisil S, et al. 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. Leukemia. 2016; 30 (5): 1044-1054.
16. Rea D, Ame S, Charbonnier A, Coiteux V, Cony-Makhoul P, Escoffre-Barbe M, et al. Management of the cardiovascular disease risk during nilotinib treatment in chronic myeloid leukemia: 2015 recommendations from the France Intergroupe des Leucémies Myéloïdes Chroniques. Bull Cancer. 2016; 103 (2): 180-189.
17. Stève-Dumont M, Baldin B, Legros L, Thyss A, Re D, Rocher F, et al. Are nilotinib-associated vascular adverse events an under-estimated problem? Fundam Clin Pharmacol. 2015; 29 (2): 204-208.