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Editorial

Anagrelide and cardiovascular events. Much ado about nothing?

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Anagrelide hydrochloride (AG) is an orally quinazoline derivative that reduces the platelet count through inhibition of the post-mitotic phases of megakaryocyte development. In Europe, AG was licensed in 2004 by the European Medicines Agency (EMEA) for the reduction of elevated platelet counts in high-risk essential thrombocythemia (ET) patients who are intolerant to, or whose elevated platelet counts are not reduced to an acceptable level by, their current therapy (usually hydroxycarbamide). Several studies have demonstrated its efficacy in lowering platelet count and reducing ET-associated symptoms [reviewed in [1]]. Owing to its inhibitory effect on cyclic AMP phosphodiesterase III, AG causes positive inotropic effects and vasodilation, leading to common side effects such as headache, tachycardia, palpitations and fluid retention. Although infrequent, some serious cardiovascular (CV) adverse events (CV-AE) have been associated with AG, mainly reversible heart failure, including high-output heart failure, atypical Takotsubo syndrome and cardiomyopathy. The frequent CV side effects, as well as, in a minor degree, the fear of appearance of potentially life-threatening cardiac effects, may partially explain the variable percentage of patients who discontinue treatment, that ranges from 10% to 50% in published studies. In this background, the need and/or usefulness for exhaustive cardiac evaluation mainly by electrocardiogram (ECG) and echocardiography before starting AG or when CV-AE appear is not well defined, and different approaches varying from no cardiac evaluation to extensive cardiovascular investigation are currently being carried out. According to this scenario, some guidelines or specific recommendations about this topic would be helpful.

In this issue, the role of CV evaluation in relation to treatment with AG has been analyzed retrospectively by Gugliotta et al. [2] in 232 patients from the ET Italian Registry. With a mean treatment duration of 27 months (522 patient-years), 30% of ET patients experienced some CV-AE, with palpitations being the most frequent event (24%). AG withdrawal due to any reason was reported in 28%, but only in 4% of all patients CV-AE led to AG discontinuation. The unique variable significantly associated to CV-AE occurrence was a high AG induction dose. The main conclusions of the study are that most CV-AE were mild and easily manageable, and the lack of benefit of performing a complete cardiac evaluation as a predictor of the occurrence of CV-AE. Of interest, the authors describe the occurrence of heart failure with normal left ventricular ejection fraction in seven patients, all of whom continued with AG treatment. Besides, angina or acute myocardial infarction was seen in 12 patients, but AG withdrawal was only performed in two patients.

This study raises several matters to be considered regarding the cardiovascular effects of AG. First, the small frequency (4%) of patients who stopped AG due to CV-AE is similar to that reported by the Anagrelide Study Group in 577 patients [3]. This figure has been reported to be higher in series published after 2004, probably due to an increased awareness of these adverse effects in relation with the warnings and recommendations made by the EMEA and the pharmaceutical company who licensed the product. Moreover, the serious and fatal cases reported may also have influenced physicians in taking a conservative side effect-preventing attitude resulting in a relatively high drop-out rate from treatment. However, some authors have confirmed the safety of AG even after acute coronary syndromes [4]. Second, the role of full cardiac evaluation is difficult to assess from the results of this study. The lack of a homogeneous/well-defined policy and a prospective design make this issue complex to interpret. In spite of that, it seems reasonable to conclude from the results of this study that, at least, exhaustive cardiologic evaluation is not necessary in all patients. Finally, and to be taken into account, only prospective controlled studies having AE as the primary objective can be of value for assessing the frequency and seriousness of complications related to therapy, since spontaneous registers usually give underestimates of the true frequency and severity.

In our opinion a basic cardiac evaluation should be performed before starting AG treatment (Fig. 1). This should include cardiovascular risk factors assessment, medical history with reference to previous cardiac diseases and symptoms (angina, dyspnea, syncope), and ECG. This test is easy to perform, its abnormalities may warrant further cardiac investigation, and if the patient presents AG-related palpitations, having a baseline ECG can be very useful for comparison. Additional testing is not needed in most patients, but in the case of cardiac-related symptoms, ECG abnormalities or previous ischemic or valvular heart disease, further evaluation is mandatory. In this case, other tests can comprise echocardiography, exercise testing and referral to a cardiologist. Also, bearing in mind the inotropic and chronotropic properties of this drug, it would seem prudent to avoid AG use in those patients with heart failure.

If the patient presents AG-related palpitations, an ECG examination during a period where symptoms are present will help to differentiate benign from arrhythmic etiology (Fig. 2). In case of symptoms occurring within a 24-h period, simple Holter

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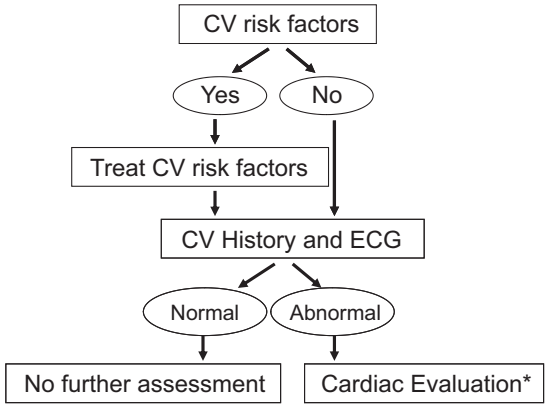

Fig. 1. Cardiac evaluation before initiating anagrelide treatment.

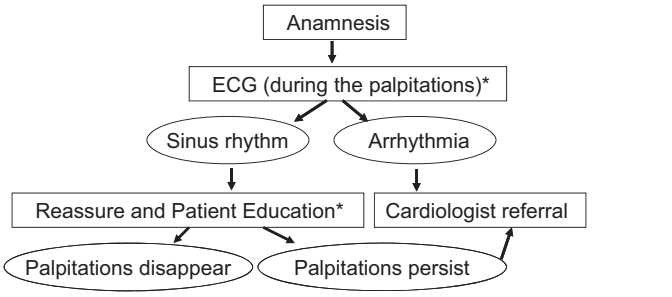

Fig. 2. Management of palpitations in patients treated with anagrelide.

monitoring is adequate to make a diagnosis. Provided that the results are normal, no further investigations are necessary and management may require not more than a review of lifestyle, patient education and reassurance. Potential non-cardiac causes, such as stress/anxiety, alcohol, and over-the-counter or prescription medications should be explored. Patients should also be advised to abstain from caffeine, as it may trigger palpitations. Drugs like beta agonists or theophylline should be avoided or used in lower doses. Low-dose β-blockers, may be useful to manage mild symptoms, mainly if palpitations are exercise or stress-related. If symptoms are more severe or persistent, referral to a cardiologist is warranted.

In summary, most CV-AE related to AG are generally mild and easily manageable with the aforementioned considerations. In the absence of pre-existing cardiac history and/or symptoms, the use of exhaustive cardiac evaluation is not necessary, although performing a baseline ECG is recommended. Treatment with AG in the setting of cardiac disease demands a close collaboration between the hematologist and the cardiologist.

Conflict of interest statement

CB has received fees in Advisory Boards from Shire; MMS has received lecture fees from Shire.

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