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Anagrelide treatment and cardiovascular monitoring in essential thrombocythemia. A prospective observational study

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ABSTRACT

In this prospective observational single-center study, 55 patients with essential thrombocythemia who were candidates for second line treatment with anagrelide (ANA) received a preliminary cardiovascular (CV) clinical, instrumental and biochemical evaluation (CV history and symptoms, CV risk factors, blood pressure, heart rate, ECG and ECHO-cardio parameters, Troponin I, NT-proBNP). After this in-depth CV screening, 54 out of 55 patients were deemed to be fit for ANA treatment. Thirty-eight of the 55 patients received ANA treatment for a median of 36 months (range 3–48), and were monitored using the same CV evaluation. Fourteen of these 38 patients manifested CV adverse events (10 palpitation, 4 edema, 2 arterial hypertension, 2 acute myocardial infarction) that were not predicted by the in-depth CV evaluation, and that led to ANA withdrawal in only one case (non-cardiac refractory edema). In conclusion, the planned in-depth CV evaluation did not appear to be necessary in ET patients to evaluate their suitability for ANA treatment, and, moreover, was not able to predict the occurrence of CV adverse events during ANA treatment. Nevertheless, the CV adverse events (mostly palpitations and edema) were easily managed by the hematologists, and required the cardiologist involvement in very few selected cases.

1. Introduction

Essential thrombocythemia (ET) is a Ph-negative chronic myeloproliferative neoplasm (MPN) characterized mostly by the occurrence of thrombo-hemorrhagic events [1]. The risk of developing such events is linked to many clinical and biological factors, including older age, history of prior thrombosis or hemorrhage, severe thrombocytosis, leukocytosis and JAK2 V617F mutation [2–7]. More recently, the presence of general cardiovascular risk factors (CVRFs) has been reported as a further relevant thrombotic risk factor [8].

Despite of a lower frequency compared to ischemic neurological events, the thrombotic CV events, associated with the neoplastic disorder per se and with the presence of thrombotic risk factors [8–10], are reported in over 10% of ET patients [2,11,12].

Non-thrombotic CV adverse events (CVAEs) have been reported with different frequencies in ET patients receiving cytoreductive drugs, including interferons alpha (IFN), and anagrelide (ANA) [13–17]. Palpitations/tachycardia are common CVAEs, both with IFN and ANA; arterial hypertension, congestive heart failure, arrhythmia, atrial fibrillation, supraventricular or ventricular tachycardia, and syncope are uncommon CVAEs with ANA; angina,

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acute myocardial infarction, cardiomyopathy, pericardial effusion, vasodilation and postural hypotension are rare CVAEs, both with IFN and ANA.

ANA is a drug that selectively lowers the platelet count. Due to the inhibition of phosphodiesterase III, ANA exerts inotropic, chronotropic, and vasodilator effects; these properties may contribute to CVAEs, which in some cases lead to the treatment discontinuation [18–27].

The 2004 Italian guidelines on ET therapy, considering the peculiar pharmacological characteristics of ANA, recommended the acquisition of data on ANA efficacy and safety, either through enrolment of patients in therapeutic trials or by collecting data in disease registers [3]. Moreover, in the same year, the European Medicines Evaluation Agency (EMEA, now EMA) registered ANA (Xagrid, Shire Pharmaceuticals) as a second line treatment in ET, with an explicit recommendation for pre-treatment CV examination (including ECG and ECHO-cardiography), and CV monitoring during treatment [17].

The observational European study EXELS (Evaluation of Xagrid Efficacy and Long-term Safety) [28] registered also data on ANA CV safety, but the pre-ANA CV instrumental evaluation was performed only at discretion of the investigators. The retrospective study of the Registro Italiano Trombocitemie (RIT), which focused on the CV aspects of ANA treatment in 232 ET patients, showed that the CVAEs (mainly palpitations) were associated with ANA withdrawal in a small percentage of cases (3.9%), and that the CV instrumental evaluation, inconstantly performed, did not predict the CVAEs [29]. The present prospective observational single-center study of the RIT was designed and conducted in order to define the role of a routine in-depth clinical, instrumental, and biochemical CV evaluation performed in ET patients before and during ANA treatment.

2. Materials and methods

2.1. Patients

Patients diagnosed with ET (PVSG or WHO criteria) in the RIT Centre of Reggio Emilia, who were candidates for ANA treatment in accordance with current therapy guidelines [3–6], were enrolled in this prospective observational study. Informed consent was obtained in accordance with the local Ethical Committee.

2.2. Study plan

The aim of the study was to perform an in-depth CV screening on at least 50 consecutive patients, in order to assess their suitability for the ANA treatment. Moreover, for patients actually starting the ANA treatment, a CV monitoring was planned for at least 1 year (maximum 4 years), with intervals of 6-month in the first year and 12 months thereafter.

2.3. CV evaluation

The clinical, instrumental, and biochemical CV evaluation, both at the screening and during the monitoring phase, was planned to identify both minor cardiopathies (valve abnormalities of minimal/low degree, without symptoms and with no evidence of clinical or hemodynamic signs), and major cardiopathies (congenital or acquired structural abnormalities involving the cardiac valves and/or the cardiac muscle with associated cardiac failure), that could affect the CV safety during ANA treatment.

2.3.1. CV clinical evaluation (CVCE)

In the screening phase, the CVCE was based on: CV history; CVRFs including arterial hypertension (AH), smoking, diabetes, hypercholesterolemia; ongoing CV drugs (e.g., ACE inhibitors, angiotensin receptor blockers, beta blockers, diuretics, lipid lowering drugs); CV symptoms; CV physical examination with registration of heart rate (HR) and blood pressure (BP).

During ANA treatment, the CVCE considered in particular: CV symptoms; ongoing CV drugs; CV physical examination with registration of heart rate (HR) and blood pressure (BP).

2.3.2. CV instrumental evaluation (CVIE)

The CVIE, both at the screening and during the monitoring phase, included the electrocardiogram (ECG) and the echocardiogram (ECHO), and, where indicated, further specific tests such as ECG Holter Monitoring, exercise or pharmacological Stress Test, BP Holter Monitoring, ECHO-CT scan.

2.3.3. CV biochemical evaluation (CVBE)

The CVBE was based on the plasma level measurement of Troponin I (TnI), and N-Terminal pro Brain Natriuretic Peptide (NT-proBNP).

2.4. Hematological monitoring

The hematological monitoring, performed during the routine visits at most every three months, included the evaluation of platelet count (PLT $\times 10^9$/L), white blood cell count (WBC $\times 10^9$/L), hemoglobin level (Hb, g/dL), and hematocrit level (HCT%), together with the registration of ANA doses (in induction and maintenance phases), thrombo-hemorrhagic complications and disease evolution.

2.5. Statistics

All statistical analyses were performed using STATA software, version 10.1, and Microsoft Excel 2007, and were used to assess patient parameters at diagnosis, at CV screening, and during the CV monitoring phase.

The analysis considered also the main hematological and CV parameters in the patients with and without occurrence of CVAEs during the anagrelide treatment. The categorical variables were analyzed with between-group comparisons, using the chi-square or Fisher's exact test where appropriate. Summary statistics (*N*, median, minimum and maximum) are reported for continuous variables, and they were compared by Kruskal–Wallis test as appropriate. Univariate linear regression models were estimated to investigate the variation of the hematological variables during the monitoring phase.

P-values less than or equal to 0.05 were considered significant (one side for chi-square tests and two sides for all other tests).

3. Results

3.1. Patients

Fifty-five ET patients, 26 males and 29 females, were enrolled in this study between November 2007 and October 2011. At diagnosis, median age was 43 years (range 19–67), and median PLT count was 782 $\times$ 10^9/L (range 498–1518). JAK2 V617F mutation was documented in 30 (54.5%) cases. In accordance with current guidelines on ET therapy [3–6], after diagnosis all patients received a cytoreductive treatment, and 49 (89%) of them received an antiplatelet treatment (low dose aspirin in 45 cases). Among these 55 patients, due to poor hematological response (31 cases) and poor tolerance (24 cases), a switch from the ongoing cytoreductive drugs to anagrelide treatment was considered, and consequently the study-planned CV screening was performed (Table 1).

Table 1
General and hematological data of the 55 patients at the CV screening.

Males/females	26/29
Age, years, median (range)	49 (31–77)
Time after diagnosis, months, median (range)	68 (3–191)
Previous cytoreductive therapy, pts	55 (100%)
HC/HC + other/IFN/BUS, pts	30/12/12/1
Antiplatelet treatment, pts	49 (89%)
ASA low dose/Ticlopidine, pts	45/4
PLT $\times 10^9$/L, median (range)	656 (317–1046)
WBC $\times 10^9$/L, median (range)	6.8 (2.8–17.0)
Hb g/dL, median (range)	13.7 (9.2–16.0)
HCT %, median (range)	41 (33–50)

ASA, acetyl salicylic acid; HC, hydroxycarbamide; IFN, interferon alpha; BUS, busulfan.

3.2. CV screening

The main CV data of the 55 studied patients are reported in Table 2.

The CV clinical evaluation documented: history of CV disease (ablation for supraventricular paroxysmal tachycardia) in one patient; CVRFs in 38 patients (CVRFs $\geq$ 3 in 4 cases); median systolic and diastolic BP 130 mmHg (range 90–170) and 80 mmHg (range