

Case Report

Acute Coronary Syndrome in Essential Thrombocytosis is not a Contraindication *Per Se* to Anagrelide Therapy

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Introduction

Essential Thrombocytosis (ET) is a haematological neoplasia and its primary clinical impact is the increased risk of developing a thrombotic or a haemorrhagic event because of uncontrolled Platelet (PLT) count and/or PLT dysfunction. Moreover, the prolonged exposure over time to uncontrolled PLT count fluctuations contributes to the risk of developing thrombotic/haemorrhagic events.

The management of this chronic myeloproliferative disorder includes mainly cytostatic drugs (alkylators) such as hydroxyurea, busulfan or pipobroman. However these drugs carry many side effects including the risk of triggering leukemogenic events. After the discovery of somatic mutations involving the Jak-2, MPL and (more recently) the calreticulin gene, tyrosine kinase inhibitors and other targeting agents have been developed. However, these novel drugs have not been approved for clinical use in ET patients so far. Therefore, anagrelide still represents a valuable alternative drug capable of controlling platelet count in ET without carrying a cancerogenic risk. This drug is a phosphodiesterase inhibitor and has been reported to cause several cardiac side effects such as palpitations, myocardial dilatation [1], Takotsubo syndrome (ventricular contractile dysfunction with akinesia) [2] and even acute myocardial infarction (MI). For these reasons clinicians have been reluctant to prescribe anagrelide in ET patients with any cardiac co morbidity.

We report on an ET patient who after developing a MI was successfully treated with anagrelide. No cardiac toxicity was seen after using the drug.

Case Report

A 55 year-old woman developed an MI in 2011, involving a

monovascular coronary entry with critical stenosis of the medial and proximal anterior arteries. This was treated with Percutaneous Transluminal Coronary Angioplasty (PTCA) and Drug Eluting Stent implantation (2.75 x 30 mm) on dual platelet anti aggregation with good revascularization results. On this occasion her PBC revealed severe thrombocytosis with PLT 1941.000/uL, Hb 12.5 g/dL and WBC 12.000/uL. Liver and renal function tests were normal. Bone marrow cytology and histology were consistent with ET. Cytogenetic tests showed a normal karyotype. Molecular analysis showed homozygosity (62%) for the JAK2-V612F mutation. Splenomegaly, 4 cm below the costal margin was documented. A comorbid history of hypertension with β -blocker treatment, nebivolol 5mg OD, was recorded. Risk factors for cardiovascular disease such as smoking, diabetes and hypercholesterolemia were absent. Echocardiography showed a reduced ejection fraction but still above 55%. The patient was started on hydroxyl urea 0.5 gr OD, which was slowly increased to 1.5 gr OD. Her PLT count remained relatively well controlled below 400.000/uL until May 2013 when she developed severe ulceration on her left ankle. For this reason treatment with hydroxyl urea was discontinued and the patient was started on anagrelide 0.5 mg OD, which was slowly increased to 1.5 mg OD. The drug has been well tolerated for over 1 year now without any signs of cardiovascular events or cardiac failure. Currently her PLT counts remain well controlled on anagrelide 1.5 mg OD fluctuating between 300.000 and 450.000/uL.

Discussion

Previous studies have shown that anagrelide has been associated with declarative and hypokinetic cardiomyopathy [1] [3] and Takotsubo syndrome with reversible ventricular contractile dysfunction including akinesia and expansion of apical segments and hyperkinesis of the basal segments [2]. For these reasons reduced cardiac output is believed to be a contraindication for anagrelide. Recently, a large Italian retrospective study on anagrelidecardiotoxicity showed that anagrelide cardiotoxicity consists mainly of palpitations without serious arrhythmias [4].

This case highlights firstly that anagrelide is a drug capable of controlling PLT count in ET, even post MI, provided that the cardiac ejection fraction is not significantly reduced and that coronary vascular flow is fully established by PTCA. The co-medication of a β -blocker helps to reduce oxygen consumption, to improve inotropism and improves control of palpitations. The risk of developing a secondary MI in ET due to uncontrolled PLT count can certainly justify the use of anagrelide. Furthermore, we would like to stress that clinicians before prescribing other alkylation agents (such as busulphan or pipobroman) following hydroxyl urea, should also consider the synergistic leukemogenic activity of these drugs as reported in the literature [5]. Anagrelide is not an alkylation agent and has not been associated with leukemogenesis. However, it has been recommended to perform a bone marrow biopsy before starting anagrelide to

rule out the presence of any underlying primary myelofibrosis [6]. Acute coronary syndrome in ET should be considered the epiphenomenon of an ongoing vascular damage aggravated by the co-existence of cardiovascular risk factors (smoking adipositas, diabetes, hypercholesterolemia, etc.) and by a prolonged exposure to uncontrolled thrombocytosis. Anagrelide alone or in association with other drugs is capable of controlling thrombocytosis, and should not be withheld in case of a normal cardiac ejection fraction following cardiovascular events. However, a higher bleeding risk has been observed for patients receiving treatment with anagrelide in combination with low-dose aspirine [7] implicating that this drug combination should be used cautiously in patients with a history of bleeding.

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