Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 6 (55) No. 2 - 2013

DIFFICULTIES IN THE TREATMENT OF ESSENTIAL THROMBOCYTHEMIA

R.G. MIHĂILĂ[1] S. MARCHIAN[1]
M. CERNUŞCĂ-MIȚARIU[1] R.C. CIPĂIAN[1]

Abstract: *In essential thrombocythemia there is an inflammatory status, which predisposes to genomic instability and atherosclerosis development. The treatment of essential thrombocythemia may have adverse effects some of them may influence the development of associated diseases. A patient diagnosed with essential thrombocythemia 9 years ago showed liver cytolysis during the therapy with hydroxyurea. An increase in blood pressure was showed after stopping it and introducing anagrelide. The solution was combined treatment with lower doses of each product for the diminishing of side effects.*

Key words: *anagrelide, essential thrombocythemia, hydroyurea.*

1. Introduction

Diagnosis of essential thrombocythemia is often suspected when conducting a complete blood count as part of the periodic medical examination or during investigation of another condition. It is unfortunate that often the diagnosis is established only after the occurrence of thrombotic complications. Monitoring these patients should consider the possibility of the existence or occurrence of an associated cancer and atherosclerosis with its various locations to which they are particularly susceptible due to a frequent inflammatory status present in this condition. Essential thrombocythemia treatment has sometimes side effects.

2. Case presentation

A female patient, aged 58, suffered nine years ago an ischemic stroke in the right carotid artery territory, after which she presented herself to the Hematology service of Emergency County Clinical Hospital from Sibiu for the investigation of a thrombocytosis ($1213000/mm^3$) discovered in Neurology. Bone-marrow biopsy showed the presence of proliferation of megakaryocytic series. Secondary causes of thrombocytosis were excluded and later, when it was possible, the presence of JAK2V617F mutation was determined, which was positive in homozygous variant.

She received therapy with hydroxyurea in doses up to 2-2.5 g/day given as a single dose in the evening, 5 days/week, but she developed, progressively, elevations of

[1] "Lucian Blaga" University of Sibiu.

serum transaminases (alanine aminotransferase up to 88 U/L and aspartat aminotransferase up to 70 U/L) in the absence of markers of infection with hepatitis B and C virus, ethanol consumption, or potentially hepatototxic medication. Silymarin did not influence their level.

Five years later, when anagrelide became available in Romania, the dose of hydroxyurea was gradually decreased and anagrelide therapy was started at doses which progressively increased, weekly, up to 2.5 mg/day, when she could give up hydroxyurea because platelet count was normal; serum level of transaminases was normalized (alanine aminotransferase 21 U/L and aspartat aminotransferase up to 19 U/L).

But, the values of systemic blood pressure, which until then were controlled with medication have increased and increasing doses of antihypertensive preparations or changing antihypertensive classes could not control them effectively. There was even an episode of epistaxis, which imposed the need for a nasal tamponade.

Therefore, anagrelide doses were reduced and hydroxyurea was associated, drug combination under which platelet count was normal (312000/mm^3) and blood pressure could be maintained within normal limits with peridopril 5mg/day, indapamide 1.5 mg/day and 5 mg felodipine 2 times/day, and the level of transaminases do not exceed 50 U/L.

The patient has also got hypercholesterolemia, which has been corrected by diet until recently, but it increased to a maximum of 251 mg/dl in recent months, which is why, in addition to resveratrol (25 mg/day, treatment that she follows since 1 year), we associated simvastatin - 20 mg/day in the evening.

3. Discussion

There is a chronic inflammatory state in essential thrombocythemia. It is possible, at least in some cases, it may have contributed to the emergence of essential thrombocythemia, too, through the increased oxidative stress in bone marrow [1] and genomic instability [2]. Genomic instability favors the progression of essential thrombocythemia to myelofibrosis [3]. Genomic instability is also involved in development of new hematologic or non-hematologic [4] cancers (second, third neoplasia to the same patient) [2], and contributes to the progression of atherosclerosis [2, 3].

Apart from essential thrombocythemia, the patient has got dyslipidemia that has to be treated (it has a history of ischemic stroke and dyslipidemia increase thrombotic risk in patients with essential thrombocythemia). In addition, although the patient is not older than 60 years, the fact that she has got a history of a thrombotic event, it predisposes her to develop new thrombosis, whether thrombocytosis is not controlled. On the other hand, a platelet count of more than 1500000/mm^3 prones to bleeding [5]. Often, patients with essential thrombocythemia die from complications of atherosclerosis, if hematological malignancy do not progresses to acute leukemia or primary myelofibrosis.

Anagrelide therapy is indicated to patients intolerant to hydroxyurea [5], including those with hepatocytolysis, as our patient was (a rare complication of therapy with hydroxyurea). Anagrelide is effective to most patients with essential thrombocythemia or thrombocytosis accompanying other chronic myeloproliferative malignancies. In a recent study, 86.9% of patients with above

mentioned diseases obtained complete (platelet count below 450000/mm^3) or partial response after one year of treatment with anagrelide [6]. The monitor of patients receiving therapy and its adaptation depending on individual tolerance and side effects that may occur is beneficial to patients. Anagrelide therapy resulted in a 2-fold decrease in arterial thrombotic accidents, 3-fold in those produced in microcirculation and 6.6-fold in venous thromboembolism compared with the patient's history before anagrelide [6].

Anagrelide is not inferior to hydroxyurea on prevention of thrombotic complications [7]. The drug has also positive inotropic and vasodilatory effect and, sometime it may produce hypotension and, even more rarely – hypotension; in addition - diarrhea, headache, tachycardia, abdominal pain, nausea, edema, arrhythmias, and others [8]. Anagrelide may have mild or moderate adverse effects that usually do not require stopping the drug [9]. A solution to the presented patient may be alpha-interferon therapy [3], but it is not yet provided in the protocols of the National Health Insurance Romania. The link between chronic inflammation, atherosclerosis and a possible secondary cancer advocates the use of statins and alpha-interferon [3]. If the patient's disease progresses to primary myelofibrosis, the treatment with an inhibitor of Janus kinase 1 and 2, as ruxoilitinib (which has been approved by the FDA for myelofibrosis with intermediate or high risk, recently) [10] will enter into discussion.

References

1. Hasselbalch, H.C.: *Chronic inflammation as a promotor of mutagenesis in essential thrombocythemia, polycythemia vera and myelofibrosis. A human inflammation model for cancer development?* In: Leuk Res. **37** (2013) No. 2, p. 214-220.
2. Scott, L.M., Rebel, V.I.: *JAK2 and genomic instability in the myelo-proliferative neoplasms: a case of the chicken or the egg?* In: Am J Hematol. **87** (2012) No. 11, p. 1028-1036.
3. Hasselbalch, H.C.: *Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis: is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer?* In: Blood. **119** (2012) No. 14, p. 3219-3225.
4. Frederiksen, H., Farkas, D.K., et al.: *Chronic myeloproliferative neoplasms and subsequent cancer risk: a Danish population-based cohort study.* In: Blood. **118** (2011) No. 25, p. 6515-6520.
5. Alvarez-Larrán, A., Cervantes, F., et al.: *Treatment of essential thrombocythemia*. In: Med Clin (Barc). **141** (2013) No. 6, p.260-264.
6. Penka, M., Schwarz, J., et al.: *The effectiveness of anagrelide treatment in patients with Ph¬negative myeloproliferative diseases: influence on the incidence of thrombosis in the data from the Registry of patients with essential thrombocythemia and thrombocythemia associated with other myeloproliferative diseases treated with Thromboreductin® to the end of 2012.* In: Vnitr Lek. **59** (2013) No. 6, p. 516-531.
7. Gisslinger, H., Gotic, M. et al.: *Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET Study, a randomized*

controlled trial. In: Blood. **121** (2013) No. 10, p. 1720-1728.

8. Pescatore, S.L., Lindley, C.: *Anagrelide: a novel agent for the treatment of myeloproliferative disorders.* In: Expert Opin Pharmacother. **1** (2000) No. 3, p. 537-546.
9. Okamoto, S., Miyakawa, Y., et al.: *Open-label, dose-titration and continuation study to assess efficacy, safety, and pharmacokinetics of anagrelide in treatment-naïve Japanese patients with essential thrombocythemia.* In: Int J Hematol. **97** (2013) No. 3, p. 360-368.
10. Chen, X., Williams, W.V., et al.: *Population pharmacokinetic analysis of orally-administered ruxolitinib (INCB018424 Phosphate) in patients with primary myelofibrosis (PMF), post-polycythemia vera myelofibrosis (PPV-MF) or post-essential thrombocythemia myelofibrosis (PET MF).* In: J Clin Pharmacol. **53** (2013) No. 7, p. 721-730.