THE POSSIBLE ASSOCIATION OF MONOCLONAL GAMMOPATHY OF UNDETERMINED SIGNIFICANCE AND JAK2-V617F POSITIVE CHRONIC MYELOPROLIFERATIVE NEOPLASM

Toni Valković

Department of Hematology, Rijeka University Hospital Center, Rijeka, Croatia

Dear Editor,

I have noticed a possibly coincidental, but intriguing issue, previously investigated by some authors, which I would like to re-actualize and share with hematological community as an impulse for future investigations and potential clinical trials.

Among 29 patients of mine with the diagnosis of JAK2-V617F positive chronic myeloproliferative neoplasm (CMPN), including polycythemia vera (PV), essential thrombocythemia (ET) and idiopathic myelofibrosis, two of them developed monoclonal gammopathy of undetermined significance (MGUS), which seems to be a higher frequency than expected in the general Caucasian population.

Patient 1: A Caucasian female, diagnosis of PV was established in 1997, according to the Person-Messinazy's criteria[1], when she was 65. She was treated with periodical venesections, aspirin and hydroxycarbamide (HC). Later on, JAK2-V617F mutation was proven. In 2007, she transformed into myelofibrosis and MGUS, IgG lambda, was diagnosed using the International Myeloma Working Group criteria[2]. The patient died in 2011 due to myelofibrosis progression.

Patient 2: A Caucasian male, diagnosis of PV was established in 1997, when he was 55. He was treated in the same way as Patient 1, with periodical venesections, aspirin and HC. During the course of disease, JAK2-V617F mutation was confirmed. The diagnosis of MGUS, IgG kappa, was made in 2009. The same diagnostic criteria for PV and MGUS were used. The patient is stable and under control, there has been no progression/transformation of PV or MGUS.

This observation on a very small group of patients cannot be a basis for any conclusions. However, the metachronous development of MGUS in patients with long-lasting JAK2-V617F positive PV (CMPN) treated with HC for years, can implicate several questions:

1. Can the long-lasting use of HC increase the incidence of MGUS in patients with PV (CMPN)?

2. Can the JAK2-V617F mutation somehow be involved in the pathogenesis of MGUS in such patients?

3. Is it possible that bone marrow fibrosis, which appears and progresses during the biological course of PV (CMPN), may promote the development of monoclonal plasma cells due to changes in bone marrow microenvironment, especially fibroblast activity?

4. Finally, is the risk of MGUS development higher in patients with PV (CMPN) than in the general population?

Some authors have described patients with CMPN treated with HC who finally developed plasma cell dyscrasias or other hematologic neoplasms[3,4], but until now there has been no clear association between the use of HC and an increased risk of developing second hematologic malignancies. In their retrospective

Correspondence to: *Prof. Toni Valković, MD, PhD*, Department of Hematology, Rijeka University Hospital Center, Krešimirova 42, HR-51000 Rijeka, Croatia
E-mail: toni_val@net.hr

Received February 4, 2013, accepted March 31, 2014

analysis, Radaelli *et al*. found that patients with ET treated with HC did not have an increased risk of second hematologic tumors[5]. Still, the possible oncogenetic potential of HC remains a matter of debate.

It is well known that JAK2/STAT pathway plays a role in myeloma pathogenesis[6,7]. Furthermore, some of the JAK2 tyrosine kinase inhibitors have shown significant anti-myeloma activity[7,8]. On the other hand, Fiorini *et al*. did not find the presence of JAK2-V617F mutation in their sample of myeloma patients[9]. Taken together, further investigation of JAK2/STAT pathway, as well as mutational screening of JAK2 coding exons, are warranted in plasma cell dyscrasias. Randi *et al*. have already investigated the association of MGUS and PV/ET in their retrospective studies. They found a higher incidence of MGUS in PV/ET patients compared to control patients, although without any statistical significance[10,11]. Economopoulos *et al*. and Berner and Berrebi also noticed a potential connection between CMPN and MGUS[12,13]. However, these studies are not recent. New knowledge of the pathogenesis of CMPN, especially the finding of JAK-2 mutations, implicates the necessity of larger, prospective, well designed trials to find the so far missing association between CMPN and MGUS.

References

1. PEARSON TC, MESSINEZY M. The diagnostic criteria of polycythaemia rubra vera. Leuk Lymphoma 1996;22:87-93.
2. International Myeloma Working Group. Criteria for classification of monoclonal gammopathies: a report of International Myeloma Working Group. Br J Haematol 2003;121:749-57.
3. BEN YOUSSEF Y, GMIDENE A, BOUABID Z, BOUALLEGUI S, SRIHA B, ZAIER M, *et al*. Multiple myeloma following essential thrombocythemia. Ann Biol Clin 2013;71:457-60.
4. AZAGURY M, MARTELLI JM, MORCELET M, DUBOUCHER C, FLANDRIN G. Development of hairy cell leukemia in patient treated with cytoreductive agents for essential thrombocythemia. Leuk Lymphoma 2003;44:1067-9.
5. RADAELLI F, ONIDA F, ROSSI FG, ZILIOLI VR, COLOMBI M, USARDI P, *et al*. Second malignancies in essential thrombocythemia (ET): a retrospective analysis of 331 patients with long-term follow-up from a single institution. Hematology 2008;13:195-202.
6. SONG L, LI Y, SUN YX, YU M, SHEN BF. IL-6 inhibits apoptosis of human myeloma cell line XG-7 through activation of JAK/STAT pathway and up-regulation of Mcl-1. Ai Zheng 2002;21:113-6.
7. De VOS J, JOURDAN M, TARTE K, JASMIN C, KLEIN B. JAK2 tyrosine kinase inhibitor tyrphostin AG490 downregulates the mitogen-activated protein kinase (MAPK) and signal transducer and activator of transcription (STAT) pathways and induces apoptosis in myeloma cells. Br J Haematol 2000;109:823-8.
8. RAMAKRISHNAN V, KIMLINGER T, HAUG J, TIMM M, WELLIK L, HALLING T, *et al*. TG101209, a novel JAK-2 inhibitor, has significant *in vitro* activity in multiple myeloma and displays preferential cytotoxicity for CD45+ myeloma cells. Am J Hematol 2010;85:675-86.
9. FIORINI A, FARINA G, REDDICONTO G, PALLADINO M, ROSSI E, ZA T, *et al*. Screening of JAK2V617F mutation in multiple myeloma. Leukemia 2006;20:1912-3.
10. RANDI ML, TISON T, ZELANTE A, RUZZON E, GIROLAMO A. Polycythemia vera and essential thrombocythemia with monoclonal gammopathy: experience of a single institution. Haematologica 2001;86:769-70.
11. RANDI ML, TISON T, RUZZON E, PACQUOLA E, GIROLAMI A. Association of monoclonal gammopathy and polycythemia vera or essential thrombocythemia: study of a large cohort of patients. Ann Hematol 2003;82:214-7.
12. ECONOMOPOULOS T, ECONOMIDOU J, PAPAGEORGIOU E, DERVENOULAS J, CHRISTODOULIDES C, PAPPA V, *et al*. Monoclonal gammopathy in chronic myeloproliferative disorders. Blut 1989;58:7-9.
13. BERNER Y, BERREBI A. Myeloproliferative disorders and nonmyelomatous paraprotein. A study of 5 patients and review of literature. Isr J Med Sci 1986;22:109-12.