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## Towards a rational treatment of essential thrombocythemia, despite limited evidence and old prejudices

This issue of Haematologica reports recommendations for the therapy of essential thrombocythemia, produced by a group of experts on behalf of the Italian Society of Hematology, the Italian Society of Experimental Hematology and the Italian Group for Bone Marrow Transplantation.[1] The methodology employed for development of these recommendations is a classical one and has been previously employed for the preparation of evidence- and consensus-based practice guidelines for the therapy of primary myelodysplastic syndromes.[2]

As underlined by Barbui and co-workers,[1] essential thrombocythemia is the chronic myeloproliferative disorder with the most favorable outcome. In fact, in large cohort studies patients with this condition showed equal or only slightly shorter survival than an age- and sex-matched healthy population. By contrast, life expectancy of patients with polycythemia vera (especially if younger than 50 years) is shorter tthat that of the reference population.[3,4] The two major problems with essential thrombocythemia are thromboembolic complications, which may markedly impair quality of life, and the increased risk of developing acute leukemia.

Based on the current diagnostic criteria, essential thrombocythemia very likely includes heterogeneous conditions. While most patients have evidence of clonal hematopoiesis[5] some patients unequivocally show polyclonal patterns of X chromosome inactivation and are very unlikely to have a stem cell disorder.[6] Clearly there is a need for biological[7,8] and molecular studies that may allow clinicians to identify the very different nosological entities currently grouped under a single definition, and to treat patients according risk-adapted strategies.

There is no question that clinicians need practice guidelines for the therapy of essential thrombocythemia. One way of realizing this is to spend some time in an Outpatient Department of a referral center for patients with myeloproliferative disorder. It can be seen how patients with very similar features and risk factors receive totally different treatments, ranging from aspirin to interferon-α.

However, scientific evidence is required in order to develop rational guidelines. In the case of essential thrombocythemia, as emphasized by one of the four reviewers of the paper by Barbui and co-workers,[1] the lamentable absence of rigorous scientific evidence necessary to support such guidelines had so far prevented their formulation. According to this reviewer, rather than *practice guidelines* based on scientific evidence, the recommendations in this paper actually represent the opinion of *expert* clinicians.

There is a considerable difference between evidence-based guidelines and expert recommendations, and it is my duty as an Editor to make the average reader aware of this.[9] When scientific evidence is insufficient, recommendations represent the authors' view of the matter rather than firm, undisputable conclusions. Consequently, other experts may find some recommendations arguable.

One of the most controversial issues during the peer-review process of this paper was the following recommendation: «*For patients younger than 40 years, who are candidates for platelet-lowering therapy, either male or female with no childbearing potential, the first-line therapy should be interferon or anagrelide (grade D).*» The mechanism of action of anagrelide is still unclear,[10] and at least one study has shown that its ability to prevent thrombosis in young patients is doubtful.[11] Therefore, it is at least questionable whether this is the best treatment for young individuals who are at high risk of thromboembolic complications. As a matter of fact, Finazzi and co-workers[12] have recently concluded that «*This indirect comparison of long-term cohort studies suggests that hydroxyurea is more effective than anagrelide in preventing thrombosis in the young, apparently without an increase in leukemic risk*».

Another controversial issue is the leukemogenecity of hydroxyurea in essential thrombocythemia. This question has been specifically addressed by Tefferi[13] who concluded that published reports on the association of hydroxyurea and acute leukemia have been inconsistent, and that the strength of the association has been relatively small. Most importantly, which patient is at particular risk of developing acute leukemia under hydroxyurea treatment? An interesting relevant observation has recently been made by Marchioli and co-workers[14] in patients with polycythemia vera. They found a clear and consistent association of age with the risk of leukemia: age greater than 70 years involved a significant risk of developing acute leukemia, while treatment with hydroxyurea *per se* was not significantly associated with this complication.

Translating the information derived by the ECLAP study[14] into a rational approach to treatment of essential thrombocythemia would potentially affect the recommendations developed by Barbui and co-workers.[1] Most of their therapeutic choices in young patients were likely influenced by the Damocles' sword of hydroxyurea leukemogenecity. However, should the observations in polycythemia vera also apply to patients with essential thrombocythemia, erroneously considering hydroxyurea as a leukemogenic agent might lead to contradictory recommendations. In fact, younger patients, who are at high risk of thrombosis and have a risk of acute leukemia similar to that of the reference population, would be treated with a drug less effective than hydroxyurea in preventing thromboembolic complications.

In conclusion, the recommendations of the expert panel[1] provide a good starting point for further discussion and investigation, but useful scientific evidence must be generated before evidence-based guidelines for the therapy of essential thrombocythemia can be formulated.

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