



How safe is hydroxyurea in the treatment of polycythemia vera?

The global incidence of polycythemia vera (PV) is approximately 0.8-1.5 cases/100,000 population/year and increases linearly with age until 80, which suggests that several mutational somatic events are necessary.¹ Despite recent advances, the pathogenesis of PV remains far from clear (see a recent review in this journal).^{2,3} Irrespective of the pathogenetic mechanism at the hematopoietic stem cell level, the final result is an excessive production of mature blood cells, in particular of erythrocytes and platelets. These represent risk factors for thromboembolic complications in PV. The increased hematocrit has been clearly associated with thrombosis, particularly in the cerebral circulation, while platelet count is a possible but not yet clearly established predictor of vascular complications.⁴ Clinical predictors of thrombosis include increasing age and a previous history of vascular events.

Current guidelines for the management of patients with polycythemia vera derive from a few clinical trials and several uncontrolled clinical studies.⁵ Therapeutic strategies for patients with PV include cytoreductive treatments (phlebotomy, cytoreductive drugs, ³²P) and antithrombotic drugs.

Among cytoreductive treatments, phlebotomy is associated with poor compliance and an increased incidence of thrombosis in the first three-five years, whereas chemotherapy may induce a higher risk of secondary malignancies after seven-ten years of follow-up. New cytoreductive drugs virtually devoid of mutagenic risk include α -interferon and anagrelide, but their role in reducing thrombotic complications or mortality remains to be demonstrated.

Until recently hydroxyurea was considered a safe drug, at least with respect to mutagenic risk. As a matter of fact most clinicians still treat PV patients with a combination of phlebotomy and hydroxyurea. However, Najean and Rain have provided evidence that hydroxyurea significantly increases the risk of leukemia both in young and old patients.^{6,7} Najean again underlined this risk at last year's meeting of the *Asociación Española de Hematología y Hemoterapia*.⁸ This issue reports another case of acute myeloid leukemia occurring in a patient with polycythemia vera in treatment with hydroxyurea (p. 755-756).

Studies from the *Gruppo Italiano Studio Policitemia Vera* (GISP) have assessed the tolerability of low-dose aspirin in PV patients (see a review by Barbui and Finazzi⁹). These studies created a basis for launching a European collaborative clinical trial (ECLAP study) aimed at testing the efficacy of low-dose aspirin in preventing thrombosis and prolonging survival in patients with PV.

In view of the available clinical evidence is it possible to make a choice facing a PV patient? Let us first state that phlebotomy remains the initial treatment in almost all patients in order to achieve rapid reduction of the expanded red-cell mass and excessive risk of thrombosis in this period. Any of us who has illustrated the risk of leukemia to a PV patient knows that the patient will be very reluctant to receive hydroxyurea. On the other hand, if one considers quality of life and costs, long-term treatments with α -interferon or anagrelide are not feasible. So, what should be done?

One might categorize patients according to age and follow the indications set out below:

Patient's age	Treatment(s) of choice
< 50 years	Phlebotomy (with the goal of maintaining hematocrit < 0.45 L/L) + low-dose aspirin Patients should be fully informed about the fact that the effect of interferon treatment on the incidence of thromboembolic complications, quality of life and survival has yet to be established, and that this drug has not negligible side effects. The individual patient should then participate in the decision making process about the administration of α -interferon.
50-70 years	Phlebotomy (with the goal of maintaining hematocrit < 0.45 L/L) + low-dose aspirin, provided that the platelet count does not exceed $1,000 \times 10^9/L$ and that there is no other risk for thrombosis (use warfarin instead of aspirin in patients with recurrent venous thromboses). Cytoreduction is indicated in all patients at high risk of thromboembolic complications. After fully informed consent, patients can be treated with hydroxyurea or α -interferon.
> 70 years	Phlebotomy as initial treatment followed by ³² P or by administration of hydroxyurea.

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Autologous bone marrow transplantation for chronic myeloid leukemia

In this issue, Meloni *et al.* report on a clinical study showing that Ph negative hematopoietic progenitors can be collected from patients with chronic myeloid leukemia (CML) responsive to α -interferon (IFN- α) and can be used to rescue the hematopoietic activity after high dose chemotherapy (p. 707-715). It is well established that CML patients may have residual normal hematopoietic stem cells at clinical onset. Recently Frassoni *et al.* reported that normal hematopoietic progenitors are relatively well preserved in most newly diagnosed CML patients, but tend to decline rapidly with time. They also found that the normal hematopoietic reservoir is consistently pre-

served in patients given IFN- α early after diagnosis and achieving a stable cytogenetic response. Other studies have found that a previous treatment with interferon does not adversely affect the outcome of allogeneic bone marrow transplantation in chronic phase CML.

The autografting procedure adopted by Meloni and coworkers yielded some complete and durable cytogenetic remissions, i.e., very encouraging results. The authors, however, conclude with a word of caution, stating that patient selection is likely to be so important in their study that the results cannot be extrapolated to *average* patients. As for any other clinical problem, only prospective randomized studies will provide an answer to the question of whether autografting can prolong survival of CML patients.

References

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