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Acute leukemia in polycythemia vera

TIZIANO BARBUI

*Department of Hematology
and Oncology, Ospedali
Riuniti di Bergamo, Italy*

The clinical course of Polycythemia Vera (PV) is characterized by significant thrombohemorrhagic complications and variable risk for disease transformation into myeloid metaplasia with myelofibrosis (MMM) or acute leukaemia (AL). There is an ongoing debate whether the evolution to AL is part of the natural history of the disease or may be related to the use of cytoreductive agents given to control myeloproliferation. It is very likely a combination of intrinsic factors, bound to PV itself, and extrinsic factors, the drugs, may exert a role.

Acute leukemia in chemotherapy-naïve patients

Very few anecdotal cases have been reported with respect to the spontaneous occurrence of AL in PV. Spivak reviewed reports of nearly 30 cases, the great majority of whom published three decades ago. Ninety % of these patients were males with a mean age 60.5 years in contrast to those developing AL following cytotoxic agents, of whom 63% were females (data from ECLAP) with a mean age of 70.9. The median interval for the spontaneous occurrence of leukaemia was 4.8 years and in chemotherapy-treated group 6.7 years. In some of these patients, AL occurred after splenectomy, and this may reflect the evolution into MMM before the AL occurrence. As in the case of PV, sporadic cases of AL in treatment-naïve patients with Essential Thrombocythemia have also been reported. In our own experience (Finazzi *et al.*), 114 cases of high-risk ET patients were randomly assigned to no treatment or Hydroxyurea therapy. After a median follow-up of 6 years, 20 patients remained untreated and none developed AL. In the PVSG experience, only one out of 12 AL patients

was never treated with cytotoxic drugs for ET.

Although AL have been documented in rare patients, these reports indicate that PV and ET have an intrinsic risk of developing leukemia and deserve to be extensively studied. At the moment, it remains unclear whether JAK2 mutation has a role in the transformation of PV to acute leukaemia. In a very recent paper (Jelinek *et al.*) JAK2 mutation was found in a lower proportion of patients whose MMM or PV progressed to AL, and the age of AL onset was 10 years lower in patients lacking the mutation. Thus, it would seem that JAK2 mutation is not critical for transformation to the acute phase of these diseases. This interesting observation needs further studies in a larger set of patients.

Acute leukemia in treated patients

In the seminal paper by the PVSG-01 trial (Berk *et al.*), 431 patients were randomized to one of the following treatments: phlebotomy alone, radioactive phosphorus plus phlebotomy, or chlorambucil plus phlebotomy. Patients in the two myelosuppressive arms had an excess of AL, which was documented in 13% of patients in the chlorambucil arm; in contrast, the reported incidence of AL was only 1.5% in the phlebotomy arm. The latter figure would represent the natural propensity of the disease to develop AL. However, since many patients in the phlebotomy arm were shifted to chemotherapy during follow-up and it is not clear whether this factor was considered and to what extent in the final analysis, there is a suspicion that 1.5% AL incidence refers to a very selected population with less progressive disease. To reduce the rate of AL, Hydroxyurea was investigated in a phase II study. After a median of 8.6 years, 51 patients had an inci-

dence of AL of 9.8%, a figure comparable to that obtained by Najean *et al.* of 10% after 13 years. In other observational prospective studies, the estimated incidence of AL in HU treated PV patients varied between 5 to 10%. Overall, the estimated annual incidence rate was between 0.5 and 1.1. In contrast, from one randomized clinical trial by Najean, and from other observational prospective studies, the use of Pipobroman was associated with a higher risk of AL, estimated between 6% to 19% (Estimated annual incidence rate between 1.2 and 1.7).

Concerning risk-factors of AL transformation, there is no generally applicable way to predict which patient is likely to acquire this fatal complication. Initial splenic enlargement, marked leukocytosis, myelofibrotic features and abnormal karyotype are reported to be associated with this evolution. The most appropriate way to establish the role of chemotherapy would be a randomized clinical trial (RCT). However, RCT is hard to be performed in this setting, for the rarity of PV, its long-term course, the late development of AL and the unwillingness to randomize PV patients to potentially leukemogenic drugs. The prospective observational database of the large cohort of the European Collaboration on Low-dose Aspirin in Polycythemia Vera (ECLAP) study (Marchioli *et al.*; Finazzi *et al.*), in which 1638 patients were monitored using the same methodology used for a clinical trial, was a unique opportunity for a comprehensive reassessment of the risk factors for AL development in PV. In this study, the occurrence of AL was registered in 22 cases (1.3%) after a median of 2.5 years from registration and after a median of 8.4 years from the diagnosis of PV. In multivariate analysis, variables associated with the development of AL were older age and the exposure to P32, busulphan and pipobroman ($p=0.002$). The use of HU did not show a statisti-

cal difference of the risk as opposed to treatment with phlebotomy or Interferon. ($p=0.80$). However, it should be underlined that ECLAP study reflects the clinical practice in use in several European centers, and some caveats should be considered regarding the conclusion of the leukemogenic role of drugs to control myeloproliferation. In fact, their use was likely to be influenced by the aggressiveness of the disease, and this might select a group of patients more prone to haematological transformation. This work-up bias cannot be eliminated in observational studies, such as the ECLAP study, and the effect of unknown confounders, such as the biology of the disease, cannot be adjusted in multivariate analysis. In conclusion, whether leukaemia in PV is part of the natural progression of the disease, a secondary sequela of therapy or a combination of both, remains an open question. It is wise for a clinician to follow the guidelines recommendation and to limit the use of chemotherapy in high risk patients for vascular complications.

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