Is polycythemia vera a serious disease in young adults?

Thrombotic complications are less frequent in younger patients with polycythemia vera (PV) than in older ones. However, in a group of 24 patients < 45 years, 58.3% developed major thrombotic events. To decrease vascular complications while minimizing the leukemogenic risk, a consensus on the use of available therapy is necessary in such patients.

Polycythemia vera (PV) is a chronic myeloproliferative disorder usually affecting old individuals, but 4-7% of patients are younger than 40 years.[1,2] Thrombosis is the major cause of morbidity and mortality in PV, being more frequent in older patients than in younger ones (5.1 events/100 patients/year in patients > 70 years versus 1.8 in those < 40 years).[2,3] Since thrombotic events affect both quality of life and survival, the use of cytolytic treatment is considered in such cases. However, its possible leukemogenic effect must be taken into account. A few studies analyzing the clinical events and prognosis of young PV patients have been published.[1,4] We report the clinical characteristics, evolution and complications in a group of young PV patients from three Spanish institutions.

Table 1. Clinical and biological characteristics of 24 patients with PV < 45 years old.

No. of patients	24
Age (median, range)	31 (11-44)
Sex	
Males/females	9/15
Symptoms at diagnosis	
No symptoms	9
Erythromelalgia	2
Headache	6
Pruritus	4
Vision disorders/paresthesiae	1
Skin ulcers	1
Splenomegaly	16 (66%)
Hemoglobin level	
>170 g/L (females)	6/15 (40%)
>175 g/L (males)	4/9 (44%)
WBC count (>12×10⁹/L)	13/24 (54%)
Platelet count (>400×10⁹/L)	17/24 (71%)
Suggestive bone marrow biopsy features	20/22 (91%)
Spontaneous growth of erythroid colonies	11/11
Erythropoietin serum levels < 5U/L	18/18
PVSG criteria*	
3 major	15/24 (62%)
2 major + 2 minor	8/24 (34%)
2 major + 1 minor + low erythropoietin	1/24 (4%)
Thrombotic events at diagnosis	9/24 (34%)
Budd Chiari syndrome	4
Splenoportal thrombosis	3
Cerebral thrombosis	2
Thrombotic events during follow-up	5/24 (20.8%)
Budd-Chiari syndrome	3°
Cerebral thrombosis	1
Recurrent abortions	1#

**All patients had additional diagnostic criteria, such as spontaneous erythroid colonies growth/ low erythropoietin levels and/or a compatible bone marrow biopsy. °At 11, 32 and 40 months from diagnosis. #Placental thrombosis.*

PV was diagnosed in 24 subjects < 45 years old, according to the Polycythemia Vera Study Group criteria[5] with some recently introduced modifications,[6] and considering also low erythropoietin levels. Table 1 summarizes the patients' main characteristics. At presentation, 9 patients (37.5%) had major thrombotic events, including Budd-Chiari syndrome (4 cases), thromboses of the splenoportal vein tract (3 cases) and cerebral thromboses (2 cases); one patient had severe gastrointestinal bleeding, whereas nine were asymptomatic. Eighty-three percent of patients were treated by phlebotomies; hydroxyurea was administered to 46%, one patient received busulfan, and another ^{32}P. Low-dose aspirin was given to 9 patients; 3 received other antiplatelet agents. During a median follow-up of 63 months (range: 9-179), 5 additional patients (20.8%) had vascular events (Budd-Chiari syndrome, 3 cases; cerebral thrombosis and recurrent abortions due to placental thrombosis, one case each). No patient died from the thrombosis, but some became seriously handicapped. In no case was evolution to myelofibrosis or acute leukemia observed.

Thrombotic complications are the major cause of morbidity and mortality in PV. Risk factors include a previous history of vascular events and older age, with the highest risk being in patients above 70 years old. However, thrombotic events are also frequent in younger patients (< 40-45 years).[1,6] In the present study, 58.3% of patients had thrombotic complications at diagnosis or follow-up. Although none died, these complications were often life-threatening and had repercussions on the quality of life. In this sense, the present data agree with previous similar studies. Najean *et al.* reported 25.8% of patients < 40 years had thrombotic events and indeed 7 of the patients died as a consequence of the thrombosis.[1] Frezzato *et al*.[4] registered a 67% rate of thrombotic events (52% at diagnosis) in 28 PV

Table 2. Polycythemia vera in young people: results of different studies.

	Najean et al.1	*Frezzato et al.3*	*Present study*
No. of patients	58	28	24
Sex	35M/23F	20M/8F	9M/15F
Age (years)	≤40	≤40	≤45
Median follow-up (years)	(Maximum: 20 years)	8.2 (0.3-16.7)	5.3 (0.6-14.9)
Thrombotic events			
Total	25.8%	67%	58.3%
At diagnosis	15%	52%	37.5%
During follow-up	10%	43%	20.8%
Hemorrhagic events			
Total	3.4%	18%	4%
At diagnosis	1.7%	4%	-
During follow-up	1.7%	13%	4%
Evolution			
Acute leukemia	1.7%	7%	-
MF-spent*	22.4%	-	-
Mortality			
Total	17% (10/58)	14% (4/28)	–
Thrombosis	12% (7/58)	7% (2/28)	–
Acute leukemia	1.7% (1/58)	7% (2/28)	–
MF-spent*	3.4% (2/58)	–	–

**MF-spent: myelofibrosis spent phase.*

patients < 40 years, 2 of whom died from the thrombosis. Table 2 shows the main data of the above two series and the present ones.

It is well known that chronic myeloproliferative disorders, notably PV,[1,7] are the main cause of Budd-Chiari syndrome. Because of this, when the diagnosis of Budd-Chiari syndrome is made, a search for an underlying myeloproliferative disorder must be carried out. This search should include serum erythropoietin determination, culture of blood erythroid progenitors, bone marrow karyotype, and marrow biopsy since minimal features suggesting a myeloproliferative disorder are often observed.

In summary, vascular complications in young PV patients are life-threatening and can provoke clinical sequelae. This would favor the use of cytolytic agents, which is counterbalanced by a possible increase in acute leukemia. A consensus on the rational use of available therapies therefore seems necessary. In this regard, low dose aspirin can be used if platelet counts are not too high. Interferon is another possibility, given its lack of mutagenicity,[8] whereas phlebotomy plus anagrelide is an option for patients with thrombocytosis not tolerating interferon.[8,9] However, since the leukemogenic effect of hydroxyurea has not been clearly established,[10] its association with phlebotomy remains a reasonable option.

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