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Characteristics and outcomes of patients with essential thrombocythemia or polycythemia vera diagnosed before 20 years of age: a systematic review

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ABSTRACT

Although it is well known that myeloproliferative neoplasms occur in younger patients, few large cohorts of such patients have been reported. Thus, our knowledge about circumstances of diagnosis, outcome and treatment is limited, especially for children and young adults. We therefore performed a systematic review of cases, published since 2005, concerning patients aged below 20 years at the time of diagnosis of essential thrombocythemia or polycythemia vera. We identified 396 cases of essential thrombocythemia and 75 of polycythemia vera. The median age at diagnosis was 9.3 and 12 years, respectively, and females constituted 57.6% and 45% of the groups, respectively. Half of the patients were asymptomatic at diagnosis. The proportion of so-called triple negativity was high: 57% in essential thrombocythemia and 73% in polycythemia vera. The incidence of thrombosis during the follow-up was 9.3% in patients with polycythemia vera and less, 3.8%, in those with essential thrombocythemia. Venous events were predominant (84.2%), with hemorrhagic episodes being rarer (<5%). The risk of evolution also seemed low (2% to myelofibrosis and no reports of acute leukemia), but the median follow-up was only 50 months. Survival curves were not available. Half of the patients received an antithrombotic drug and 40.5% received a cytoreductive drug. All data should be analyzed with care because of the proportion of missing data (10.7% to 74.7%). This review highlights interesting points concerning this population of young patients with myeloproliferative neoplasms, including that such patients were identified as negative for all common driver mutations, but also shows the need for larger contemporary cohorts with longer follow-up to assess the true prognosis of these patients.

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Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are the most prevalent myeloproliferative neoplasms (MPN). However, the median age at diagnosis of both conditions is over 60 years. Patients with these diseases are particularly exposed to risks of thromboembolic events and evolution into more aggressive disorders (myelofibrosis, myelodysplastic syndromes and acute myeloid leukemia), with a consequent heavy burden of morbidity and mortality.[1]

Current clinical guidelines concerning the diagnosis and management of ET and PV are generally written for older patients and emphasize that testing for a driver mutation and a bone marrow biopsy are fundamental to diagnose an MPN and that treatment should be adapted according to a classification into low risk or high risk based on the patients' age and history of thrombosis or hemorrhage (prescription of aspirin and cytoreductive drugs) in order to reduce the occurrence of thrombosis.[2-4]

Details of some large cohorts of young patients with MPN, defined sometimes as below 60 and at other times as below 40 years old, have already been published.[5-8] Notwithstanding these publications, there are only sparse data concerning very young patients with MPN (aged below 20 years at diagnosis), particularly regarding details such as initial characteristics (reason for consultation, clinical features, bone marrow biopsy features) and outcomes (thrombosis, pregnancy, disease evolution, incidence of second cancer and survival). Furthermore, the utilization of therapeutic modalities in this population is largely unknown. For example, the proportions of very young patients treated with antiplatelet and/or cytoreductive therapies and the therapeutic goals are very poorly defined and, furthermore, there is no information about the potential, long-term sequelae of the treatments.

Here we present a review of published cases of ET and PV patients below the age of 20 years at the time of diagnosis. The earliest data collection point we chose was 2005, coincident with important discoveries concerning the molecular pathogenesis of these conditions, so that we would have more information about the mutational status of the patients and to improve the likelihood of ruling out reactive conditions confounding the diagnosis.[9-12] We describe the biological and clinical characteristics at the time of diagnosis and the incidence of vascular and long-term complications during the follow-up.

Methods

PubMed research

The purpose of this review was to learn more about young patients diagnosed with MPN: their characteristics at diagnosis and the incidence of complications. To our knowledge there has been no systematic review of the published cases. We used PubMed (*https://www.ncbi.nlm.nih.gov /pubmed*) to identify articles related to our topic.

For this review, we analyzed papers referring only to patients with ET or PV who were under 20 years old at the time of the diagnosis. The keywords used during the research were: polycythemia vera, primary or essential thrombocythemia/thrombocytosis, myelofibrosis, myeloproliferative neoplasms or diseases, young patients/adults, children/childhood and pediatric cases. To avoid the bias of recording misdiagnosed PV cases, only papers published since 2005 were eligible, coincident with the date of the discovery of the *JAK2*^{V617F} mutation. Furthermore, we directly excluded familial MPN cases, if this was clearly specified in the title or the text. All types of articles were collected: general reviews, cohort papers (including more than 5 patients) and case reports (including fewer than 5 patients).

Selection of the articles

We identified 87 articles concerning MPN and young patients and we finally analyzed 46 articles after exclusion of redundant papers (same authors, same numbers of patients), uninformative cases (no information about diagnosis or outcomes), alternative myeloid diseases (primary myelofibrosis, acute leukemia), inadequate age identification (cohorts of young patients, but below 40 years old) as delineated in the PRISMA flowchart (*Online Supplementary Figure S1*) and the checklist (*Online Supplementary Table S1*).

In total, we identified 46 informative articles: 19 cohort papers (16 on ET and 3 on PV) and 27 case reports (23 on ET and 11 on PV, with some concerning both conditions).[9-56] We also added seven papers with useful information concerning epidemiology.[57-63]

Collected characteristics

All informative articles were printed (published articles and supplementary data) and searched data were extracted and reported in an Excel file.

The following data collected at the time of diagnosis were recorded: age, sex, circumstances of diagnosis (e.g. thrombosis), symptoms (hyperviscosity, pain, fatigue, pruritus, microvascular events), full blood count (leukocyte, hemoglobin and platelet levels), previous cardiovascular events (thrombosis and hemorrhage),

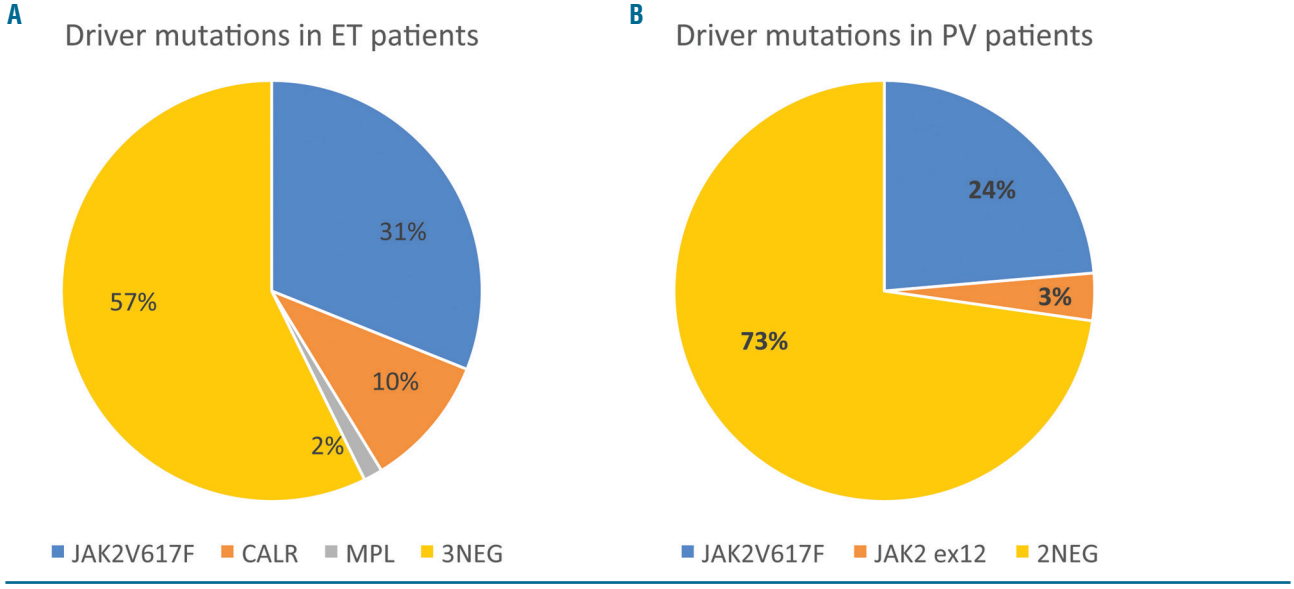

Figure 1. Driver mutations among very young patients with (A) essential thrombocythemia (n=206) or (B) polycythemia vera (n=55). ET: essential thrombocythemia; PV: polycythemia vera; 3NEG: triple negative for the *JAK*^{V617F}, *CALR* and *MPL* driver mutations. 2NEG: double negative for *JAK2*^{V617F} and *JAK2* exon 12.

molecular status (*JAK2*^{V617F} or *JAK2* exon 12, positivity for *CALR* or *MPL*, *JAK2* allele burden) and detailed molecular analysis.

The duration of the follow-up was assessed as precisely as possible, the prescribed drugs and the incidence of complications were then recorded: rate and type of antithrombotic drugs (low-dose aspirin, clopidogrel, vitamin K antagonists, heparins), rate and type of cytoreductive drugs (hydroxycarbamide, anagrelide, interferon, ruxolitinib, others), together with information on venesection requirement, incidence of cardiovascular events (thromboses and hemorrhages), evolution (ET into PV, ET or PV into secondary myelofibrosis or acute leukemia), and death. With regards to the thrombotic events, the type of vessel and the localization were recorded.

Results

Epidemiology

Only a few papers considered epidemiological data specifically for the MPN population and, it was sometimes difficult to assess the presence or absence of chronic myelogenous leukemia among the cases described. Furthermore, there was great variability in the incidence of MPN between countries (United Kingdom, Denmark, Europe, Japan), in the timing of the observation (from 1980 to 2010) and in the age of the patients (below 14 to below 25 years old).

Overall, we found that the global incidence of MPN, in children and young adults, can be estimated to be around 0.82/100,000 patients/year (range, 0.1 to 2.25): the incidence of ET is around 0.6/100,000 patients/year (range, 0.004 to 0.9), against 0.18 for PV and 0.53 for primary myelofibrosis (range, 0.003 to 1.5).

Clinical and biological data at diagnosis

Clinical characteristics

On analyzing the published literature, we were able to collect data on 471 patients, of whom 396 (84%) had ET and 75 (16%) had PV. These patients' clinical and biological characteristics are summarized in Table 1. For each described parameter, we also give the number and the percentage of data available in the published population. The median age at diagnosis was 9.3 years for ET patients and 12 years for PV patients. The percentage of female cases was also different between the two groups (57.6% in ET and 45% in PV).

The reason for the original consultation was unclear or unknown in most cases. At the time of the diagnosis, 49.6% of the ET patients and 47.5% of PV were declared to be asymptomatic. For the other patients, the two most frequent symptoms experienced were headaches (27.5% in ET and 30.5% in PV) followed by abdominal or bone pain (5.5% and 3.4%, respectively). As a potential bias, a group of 30 patients with ET were declared to suffer from microvascular disturbances but without a more precise description. Interestingly, 13.6% of PV patients and 4.7% of ET patients were diagnosed following a thrombotic or hemorrhagic event.

Splenomegaly was the most frequent abnormal sign described in the papers: 54.7% of ET and 15.3% of PV patients had a palpable spleen. Surprisingly, its presence did not seem to have induced so many abdominal symptoms as there were discrepancies between frequencies of splenomegaly and reported abdominal pain. It is also hard to understand the much higher frequency of splenomegaly in ET and the fact that this does not seem to have correlated with abdominal vein thrombosis, for example.

Table 1. Clinical and biological characteristics at diagnosis of very young patients with essential thrombocythemia or polycythemia vera.

	Essential thrombocythemia	Polycythemia vera
Number of cases (%)	396 (84)	75 (16)
Median age (years)	9.3	12
Range (years)	0.2-20	0.6-19
Male (%)	42.4	55
Reasons for consultation or symptoms, n (%)	*236 (59.6)	*59 (78.7)
Asymptomatic	117 (49.6)	28 (47.5)
Thrombosis	7 (3)	5 (8.5)
Hemorrhage	4 (1.7)	3 (5.1)
Splenomegaly	129 (54.7)	9 (15.3)
Headaches	65 (27.5)	18 (30.5)
Abdominal/bone pain	13 (5.5)	2 (3.4)
Paresthesia/erythromelalgia	11 (4.7)	1 (1.7)
Syncope	3 (1.3)	3 (5.1)
Fatigue	2 (0.8)	4 (6.8)
Pruritus	0	3 (5.1)
Full blood counts at presentation	*229 (57.8)	*67 (89.3)
Leukocytes, x 10^9/L	10.6	13.2
Hemoglobin, g/L	131	157
Platelets, x 10^9/L	1192	799
Driver mutations	*388 (98.2)	*75 (100)
JAK2 exon14, n	130	30
Allele burden, %	24.1	43.5
JAK2 exon12, n	-	2
CALR, n	23 (type1, n=9; type2, n=6)	-
MPL, n	4 (L, n=2; K, n=1)	

*indicates the number and percent of available data for each category of parameters.

Biological characteristics

The results of the full blood count at diagnosis are presented in Table 1. For ET patients, the median leukocyte count was 10.6 10^9/L, the hemoglobin concentration was 131 g/L and the platelet count was 1192x10^9/L (maximum 4500x10^9/L). For PV patients, the median leukocyte count was 13.2x10^9/L, the hemoglobin concentration was 180 g/L (maximum level, 189 g/L), the maximum hematocrit was 72.5% and the platelet count was 799x10^9/L. It is difficult to understand how hereditary thrombocytosis and erythrocytosis were excluded for these patients.

To assess the diagnosis of MPN, many authors wrote in the "Patients and methods" section that their patients fulfilled the diagnostic criteria according to the 2001, 2008 or 2016 World Health Organization classification. However, bone marrow results were described for less than 52% of the ET and 44% of the PV cases. Generally, the descriptions were short with a conclusion expressed as "compatible with MPN".

Molecular analyses

Considering the entire cohort of PV patients, we noted that only 37% and 2.5% were positive for *JAK2* exon 14 and exon 12 mutations, respectively. Three studies comprehensively assessed the presence of both types of *JAK2* mutations: the percentage of *JAK2* exon 14 cases decreased to 24% whereas, the rate of *JAK2* exon 12 mutations remained stable at 3% (Figure 1A).[9,13,24] According to these results, the percentage of patients positive for the V617F mutation in exon 14 is far less than in adults, whereas that of exon 12 is identical. Consequently, the percentage of patients who do not harbor one of these two mutations is also high: 73%. Information on *JAK2*^{V617F} allele burden was available in a small number of studies and the mean value was 43.5%. This finding of much lower rates of *JAK2* mutation in young patients with PV is also unexpected and requires a prospective evaluation, including, for example, the role of red cell isotopic studies to confirm the diagnosis.

The analysis in ET patients is more complex because of the number of mutations to test. Notwithstanding, in a global analysis, the percentages of positivity were 31.7% for *JAK2*^{V617F}, 5.6% for *CALR* and 1% for *MPL* mutations Analyzing the eight cohorts of ET patients in whom all driver mutations were tested, the proportions of positivity became 31% for *JAK2*^{V617F}, 10% for *CALR*, and 2% for MPL and so 57% of the cases were triple-negative (Figure 1B).[12,14,16,17,19,20,22,33] These percentages are quite different from those in adults, among whom there is a much higher frequency of triple-negative cases and lower percentages of *JAK2*- or *CALR*-positive cases.[64] As for PV patients, the number of studies reporting *JAK2*^{V617F} allele burden was small and the mean value was 24.1%. As discussed earlier the exclusion of hereditary cases is critical here.

Interestingly, two groups have reported the results of next-generation sequencing analyses in this population.[12,16] Among 68 patients tested the authors found that 35% did not carry any of the tested non-driver mutations. Most of the patients carried only one additional mutation. The description and the proportions of non-driver mutations are shown in Figure 2. In one study, patients with ET seemed to have more mutations than PV patients.[16] The presence of mutations belonging to the high molecular risk group and inducing worse prognosis in primary myelofibrosis is uncommon in this population (*ASXL1* in 4 cases and *IDH1/2* in 1 case).[65,66] As far as concerns young patients with ET or PV, the real clinical significance of these non-driver mutations cannot be assessed from the studies.

Outcomes and survival

Thrombotic events

As noted above, some very young patients were diagnosed with MPN because of the occurrence of a thrombotic event. The exact incidence of thrombosis at diagnosis was 14.7% and 4% in PV and ET patients, respectively. So, these events seemed quite infrequent compared to their frequency in adults.[67-68] Importantly, the incidence of thrombosis after the diagnosis of MPN decreased in the PV cohort (9.3%), but remained stable in the ET patients (3.8%) (Table 2).

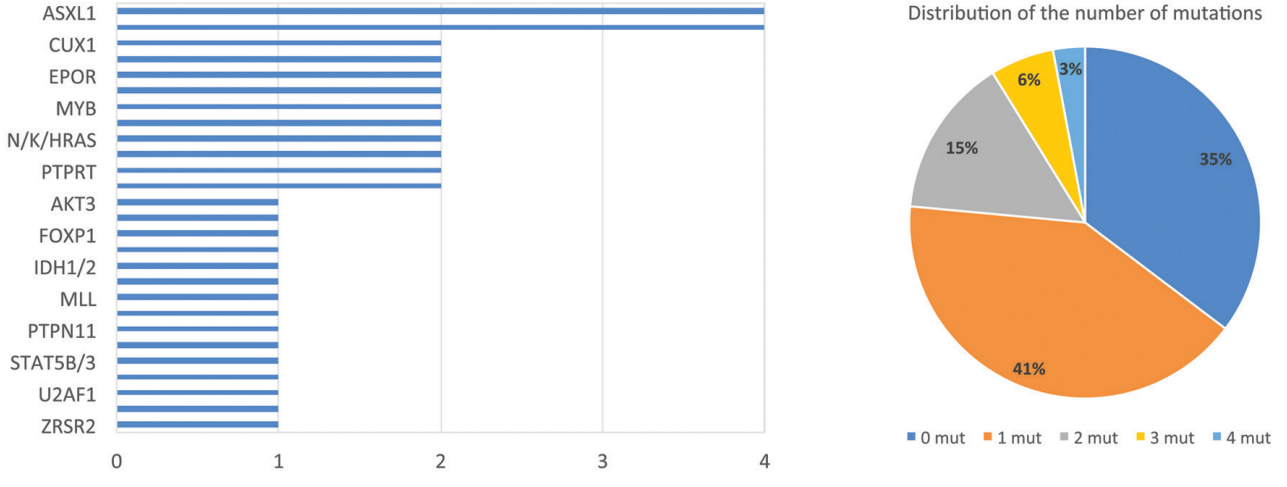

Figure 2. Description and numbers of non-driver mutations identified by next-generation sequencing in two studies (68 patients).[12,16] mut: mutations.

Global analyses of recurrence of thrombotic events are not available here since most of the data were published for entire groups and not for individuals. However, considering only the case reports (n=25), we recorded ten patients with ET who experienced a thrombotic event before or at diagnosis and only one had a recurrence during the follow up (10%). Among PV cases (n=10), five patients were in the same situation and two of them had a new thrombotic event (40%). Since this only represents a small group there is a risk of bias in these data.

Interestingly, the overall ratio of arterial/venous events (r=0.2) demonstrates a clear predominance of venous events (84.2%). This situation was identical both before and after the diagnosis. Concerning the sites of the events, thromboses of the splanchnic territories were most frequent (75% of the venous events), with a large predominance of Budd-Chiari syndrome (62.5% of all venous events). Again, this is very different from the situation in the adult population (*Online Supplementary Table S2*).

Hemorrhagic events

The number of hemorrhagic episodes seemed very low (1% before and 4.8% after the diagnosis in ET patients and 4% in both situations in PV patients). Importantly, the use of an antithrombotic drug did not seem to increase the risk of hemorrhage. The episodes described in the literature were mostly minor events, but their localization was usually unknown.

Transformation

As one of the most significant complications of MPN, transformation into secondary myelofibrosis and/or acute myeloid leukemia is a major concern. Such transformation frequently provokes a deterioration of the Performance Status and the necessity to change treatment strategy (i.e., to use ruxolitinib, allogeneic transplantation or intensive chemotherapy). Reassuringly, transformation seemed unusual in very young patients with MPN, with only 2% of cases evolving into myelofibrosis and none transforming into acute myeloid leukemia. However, this and other information about complications during the follow-up should be interpreted carefully because of the relatively short median follow-up of the cohorts and the case reports (54 and 51.3 months for ET and PV patients, respectively).

Another malignancy and long-term sequelae of therapy

Interestingly, Cario and colleagues observed that three among 36 PV patients (8.3%) were diagnosed with their MPN after having been cured from acute leukemia (2 cases) or lymphoma (1 case).[9] There are only two cohorts of patients for which the occurrence of solid cancers in the young ET and PV patients was reported, with only one case of kidney cancer observed (1/97 patients, 1%). There is no information or evidence about the potential implications of previous chemotherapy or cytoreductive drugs on the occurrence of MPN or cancer, despite the possible risk

Table 2. Treatments and outcomes of very young patients with essential thrombocythemia or polycythemia vera.

	Essential thrombocythemia	Polycythemia vera
Antithrombotic drugs, n (%)	*203 (51.3)	*59 (78.7)
Not treated	104 (51.2)	37 (62.7)
Low dose aspirin	88 (43.3)	19 (32)
Vitamin-K antagonists	11 (5.4)	7 (11.9)
Subcutaneous heparin	7 (3.4)	6 (10.2)
Cytoreductive drugs, n (%)	*239 (60.3)	* 62 (82.7)
Not-treated	112 (46.9)	6 (9.7)
Hydroxycarbamide	31 (13)	16 (25.8)
Anagrelide	50 (20.9)	0
Interferon	11 (4.6)	6 (9.7)
Venesections	0	28 (45.2)
Ruxolitinib	0	1 (1.6)
Busulfan/Melphalan/^{32}P	0	7 (11.3)
Allogeneic SCT	0	3 (4.8)
Thrombo/Erythropheresis	1 (0.4)	4 (6.5)
Complications before diagnosis, n (%)	* 307 (77)	*69 (92)
Thrombosis	16 (4)	11 (14.7)
Hemorrhage	4 (1)	3 (4)
Complications after diagnosis, n (%)	* 307 (77)	*69 (92)
Thrombosis	15 (3.8)	7 (9.3)
Hemorrhage	19 (4.8)	3 (4)
Transformation, n (%)	*264 (68.7)	*19 (25.3)
Total	7 (1.8)	2 (2.7)
Polycythemia vera	0	-
Myelofibrosis	7 (1.8)	2 (2.7)
Acute leukemia	0	0
Death (n/%)	0	3 (4)
Follow-up (months)	54	51.3

*indicates the number and percent of available data for each category of parameters. ^{32}P: radioactive phosphorus; SCT: stem cell transplantation

of these treatments modifying the genetic environment. Similarly, there are no data about the occurrence of other diseases which might be significant during the MPN, such as autoimmune, cardiac or inflammatory diseases.

Surprisingly, only one study reported data on pregnancy: six young women experienced 15 pregnancies which resulted in nine healthy babies and six miscarriages (40%). This latter percentage is much higher than in the latest cohorts of young adult women with MPN, but should be interpreted with caution.[69]

Survival and death

The mortality rate seemed low (3 cases, 0.65%): two patients died after the occurrence of Budd-Chiari syndrome despite adequate management, highlighting the fact that this event has a very high risk of morbidity and mortality, and one patient died of pneumonia that developed following a stroke. It should be noted that information about death was probably subject to reporting bias, and the median follow-up was short.

Treatments

It is not clear in the published literature whether adult or pediatric staff made decisions on these patients nor what age cut-off, if any, might have been used to decide therapy. Also, it is not clear what strategy for venesection was used for these young patients. In our review, we observed a relatively high frequency of prescription of "antithrombotic" drugs (51.2% in ET and 62.7% in PV patients). The description of the treatments is provided in Table 2. The rate of prescription of aspirin was higher in ET patients than in PV patients (43.3% *vs.* 32%) whereas, PV patients were more frequently treated with vitamin K antagonists or low molecular weight heparin (22.1% *vs.* 8.8% in ET patients, respectively). These differences were probably due to the rate of thrombosis observed among PV patients (mostly Budd-Chiari syndrome). It is difficult to know whether these medications could have been responsible for the occurrence of the hemorrhages reported during the follow-up.

As expected in this population, there was a very low number of high-risk patients (5.7%) based on a history of thrombosis (data on the number of patients with platelet counts over $1500x10^9$/L were not available). Despite the low percentage of high-risk patients, most of the subjects were treated with a cytoreductive drug or related therapy (60.8%). The description of the treatments is available in Table 2. The reasons for prescribing these treatments were not explained.

Most of the ET patients received what would be regarded as non-leukemogenic drugs, such as anagrelide (20.9%) or interferon (4.6%). Most of the PV patients were treated with phlebotomy (45.2% plus 6.5% erythropheresis), but a substantial proportion of them also received hydroxycarbamide (25.8%). The use of interferon seemed quite uncommon (9.7%), even for the pegylated formulation (one-third of the interferon-treated population). Interestingly, ruxolitinib (a *JAK1* and *JAK2* inhibitor) was prescribed in only one explicit case (three other cases were cited in a phase II trial, but without available data). Surprisingly, 16.1% of the PV patients were treated with melphalan, busulfan, radioactive phosphorus or allogeneic stem cell transplantation: most of these patients were treated in the 1980s and are represented by one cohort of patients.[9]

Discussion

We have described here the clinical and biological parameters of very young patients (aged <20 years at diagnosis of ET or PV) whose data have been published since 2005. Interestingly in this cohort of over 470 cases the clear majority (84%) had ET, which remains unexplained. Another interesting fact is that only a few cases were discovered because of the presence of symptoms (mostly headaches or migraines) or due to a thrombotic event. Importantly, the occurrence of thrombosis, hemorrhage or evolution of disease seemed quite rare.

We found that a comprehensive, or total, description of all the published cases is almost impossible. As a possible bias, some cases could also have been published in large series of young patients (under 40 years old) and we were unable to extract data specifically pertinent to our age group of interest. Furthermore, almost all the information was reported in a global way, i.e. not for individual cases and, as shown, a lot of information concerning each specific data point was lacking (the amount of missing data varied from 10.7% to 74.7%), illustrating the difficulties of our approach.

Concerning the diagnosis of MPN, bone marrow biopsy is generally regarded as essential, as illustrated recently by Putti and colleagues who demonstrated, in a descriptive study of biopsies from very young ET patients, that only 16 (76%) of the 21 bone marrow biopsies were compatible with a diagnosis of ET. Furthermore, they also confirmed the usefulness of this examination by identifying one case of PV, three cases of prefibrotic myelofibrosis and even one non-MPN case.[19] There is no such study on bone marrow biopsies among PV patients. It should be noted that there is no evidence to tell us that the management or the outcome of very young patients with prefibrotic myelofibrosis needs to be different from that of ET patients, so this remains a matter for further evaluation. In fact, it is interesting to speculate that had more biopsies been performed, the large excess of ET diagnoses may have changed.

Surprisingly, a large proportion of this cohort of young patients with MPN was found to be negative for all common driver mutations. For the patients with ET, this proportion was 57%, which is higher than that reported in adult series (between 10% to 20%).[70,71] About three-quarters of the patients with PV were also negative for any *JAK2* mutations, with the proportion varying between 63% and 75% depending on the cohorts.[9,13,24] This raises the question of whether these were real cases of MPN. As many of them were old cases, were they misdiagnosed MPN or real MPN but with different mechanisms of proliferation than the *JAK2* pathway? This suggests a potential place for next-generation sequencing in the population of patients negative for driver mutations. A new evaluation with recent cases will be useful to confirm or refute this observation.

With regards to complications, we observed a low rate of both thrombosis and transformation (4.7% and 1.9%, respectively), which is in accordance with the numbers observed in the young population in general (people aged less than 40 years old) (Table 3) but, far less than in old people.[5-8,67,68,72] Concerning the thrombotic risk, the classification of this population as a low- or very low-risk category seems appropriate (based on their age and history of thrombosis).[2] Concerning the risk of transformation, reas-

Table 3. Comparison of the characteristics of the very young patients in this cohort *versus* those of other reported series of young patients less than 40 years old with polycythemia vera or essential thrombocythemia.

	Essential thrombocythaemia					Polycythaemia vera			
	Our cohort	Boddu 2018	Palandri 2015	Lussana 2014	Barbui 2012	Our cohort	Boddu 2018	Lussana 2014	Passamonti 2003
Number	396	105	197	375	178	75	43	97	70
Median age, years	9.3	25	34	32,3	33	12	28	35	42
Age range, years	0.2-20	16-39	16-40	16-41	13-40	0.6-19	16-39	18-40	18-49
Male	42%	27%	32%	29%	38%	55%	51%	44%	70%
White blood count, 10^9/L	10.6	8.2	8.6	8.6	8.4	13.2	9.4	10.7	12
Haemoglobin, g/L	131	134	142	142	14	157	149	190	210
Platelets, 10^9/L	1192	763	850	708	796	799	547	476	544
JAK2^{V617F} cases	33.5%	53%	63%	100%	56%	40%	92%	100%	?
JAK2^{V617F} allele burden	24.1%	15	21%	?	?	43.5%	21%	?	?
Thrombosis before diagnosis	4%	6%	8%	9%	13%	14.7%	14%	12%	24%
Venous events	86%	?	68%	55%	62%	78%	?	67%	29%
Median follow-up, years	4.5	2.6	10.3	7.3	7.6	4.3	3.6	7.9	14
Thrombosis after diagnosis	3.8%	2%	10%	10%	8%	9.3%	2%	18%	11%
Hemorrhage after diagnosis	4.8%	2%	?	?	5%	4%	5%	?	?
Transformation into PV	0%	?	0%	0%	0%	na	na	na	na
Transformation into MF	1.8%	0%	5.5%	3%	3%	2.7%	0%	9%	7%
Transformation into AML	0%	2%	0.5%	0%	0%	0%	0%	3%	7%
Death	0%	8%	2.7%	0.5%	0%	4%	0%	4%	26%

PV: polycythemia vera; MF: myelofibrosis; AML: acute myeloid leukemia.

suringly, there were no cases of post-ET PV or acute myeloid leukemia, and the death rate was very low. However, we note a possible bias since most of the papers described particular data (e.g., thrombosis, bone marrow examinations, molecular analysis) as the main message, not reporting the parameters at diagnosis or detailed follow-up information; furthermore, we should also be cautious because of the short median follow-up of the patients included in this review (around 50 months). These factors could have led us to underestimate the rates of long-term complications. Thus, while the overall survival seems long, there are no published survival curves and the median follow-up, as discussed already, is quite short for this population of subjects who would normally be expected to live a further 60-70 years, if their life expectancy is similar to that of the general population.

We noted a clear prevalence of venous thrombosis with a complete inversion of the ratio of arterial/venous thrombotic events (0.2), compared to that in cohorts of adults in whom this ratio is close to 0.67 (*Online Supplementary Table S1*).[1] Interestingly, we observed a predominance of portal vein thrombosis and Budd-Chiari syndrome, mostly at diagnosis, a situation similar to that in the adult population in whom these thromboses are frequently associated with MPN and induce significant morbidity and mortality (2 of the 3 deaths reported in this review).[9] On the other hand, 83% of the arterial events occurred during the follow-up and all these events were localized in the cerebral area. Given the age of the patients and the very low supposed rate of cardiovascular risk factors (not evaluated here as unavailable), and the different mutation profiles it will be interesting to understand the mechanism of these thromboses.

Since the ECLAP study, the prescription of low-dose aspirin is highly recommended in older patients, especially with PV, to reduce the risk of thrombosis.[73] The benefit of using this drug has not been proven for either ET patients or for very young patients. Furthermore, Alvarrez-Larran and colleagues have published a retrospective study on the use of antiplatelet drugs among young (defined as less than 60 years old) patients with ET, and found that *CALR*-positive patients experienced more hemorrhages when treated with aspirin.[74] Effectively, given their metabolism, children are exposed to a higher risk of aspirin-related gastrointestinal and intracranial hemorrhages. Children below 12 years old seem particularly at risk of Reye syndrome because of the interaction between aspirin and coenzyme A reductase in mitochondria.[75,76] In Reye syndrome, gastrointestinal symptoms (nausea and vomiting) are followed by progressive encephalopathy (i.e. somnolence) until coma and death due to multi-organ failure. Unfortunately, stopping the administration of aspirin does not automatically reverse the process. The incidence of Reye syndrome among very young patients with ET and PV is unknown and there have been no published cases in the past 12 years.

According to international guidelines, in the adult ET and PV population, the prescription of a cytoreductive drug is limited to patients who are classified as being at high risk of thrombosis based on age (recommended if >60 years or younger with a cardiovascular risk factor) or platelet count >1500x10^9/L or a history of thrombosis.[2] For patients belonging to the low-risk group, no other drug than aspirin is recommended. Thus, in this very young population with low rates of prior thrombosis, aspirin should often have been the only therapy. However, the proportion of patients receiving cytoreductive drugs was unexpectedly high in this population (60.8%), and the reasons were not explained.

Given ongoing concerns about the safety of hydroxycarbamide it seems surprising perhaps that this drug was so frequently prescribed in this population of young patients. On the other hand, the relative innocuity of hydroxycarbamide has been proven in many cohorts of patients with

sickle cell disease.[77] In contrast, the use of interferons was quite uncommon even though these drugs are non-leukemogenic and the first line of cytoreductive drugs according to the European LeukemiaNet recommendations. It is important to remember that all these medications, even hydroxycarbamide, are currently unlicensed in this population. Also, there are few data concerning the side effects and the long-term consequences of the use of these drugs.

The European LeukemiaNet recommendations do not appear to have been followed closely in the population we analyzed, but at the same time, there are no adapted recommendations for the treatment of MPN in very young patients. This is potentially a substantial shortcoming since young people are not small adults and also because there is no real large cohort of patients in whom to assess the risks, outcomes and medications in a prospective manner. Thus, we propose a large pan-European study concerning very young patients. The aims of this study should be multiple: to gain a more accurate overview of the clinical and biological parameters concerning this population at diagnosis (symptoms and the way of making the diagnosis) and to obtain a clearer understanding of the incidence of thromboses, hemorrhages and disease progression. Such a study should also federate clinicians and biologists interested in the field in order to manage these patients better with the help of pediatricians.

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