Thrombocytopenia and polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome

Fiorina Giona,1 Luciana Teofili,2 Maria Luisa Moleti,1 Maurizio Martini,2 Giovanna Palumbo,1 Angela Amendola,4 Maria Gabriella Mazzucconi,1 Anna Maria Testi,1 Patrizia Pignolini,1 Sonia Maria Orlando,5 Sara Capodimonti,2 Mauro Nanni,1 Giusepppe Leone,2 Luigi Maria Larocca,3 and Robin Foà1

604 patients < 20 years of age, investigated for a suspicion of Philadelphia-negative myeloproliferative disease (MPD), were retrospectively evaluated to characterize the different forms and to examine the treatments used and long-term outcome. JAK2 mutations, endogenous erythroid colony growth, and clonality were investigated in 51 children. Mutations of thrombopoietin, the thrombopoietin receptor (MPL), and the erythropoietin receptor and mutations of other genes involved in the pathogenesis of MPD were investigated in JAK2 wild-type children. Based on our criteria for childhood MPD, we identified 34 patients with sporadic thrombocytopenia (ST), 16 with hereditary thrombocytosis (HT), 11 with sporadic polycythemia (SP), and 3 with hereditary polycythemia (HP). JAK2V617F mutations were present in 47.5% of ST and in no HT. The MPLS505A mutation was detected in 15/16 HT patients and in no ST (P < .0001). The JAK2V617F mutation occurred in 27% of SP patients diagnosed according to the Polycythemia Vera Study Group or World Health Organization 2001 criteria. Children with ST received more cytoreductive drugs than those with HT (P = .0006). After a median follow-up of 124 months, no patient had developed leukemia or myelofibrosis and 5% had thrombosis; the miscarriage rate in thrombocytopenic patients was 14%. The low complication rate in our population suggests that children with MPD may be managed by tailored approaches. (Blood. 2012;119(10):2219-2227)

Introduction

Essential thrombocytopenia (ET) and polycythemia vera (PV) are typical chronic Philadelphia-negative (Ph-) myeloproliferative diseases (MPDs) that occur in middle/advanced-age adults.1 In childhood and adolescence, these disorders are extremely rare2 and therefore published data on the clinical presentation, biologic features, treatment approaches, and long-term outcome of Ph− MPD children and adolescents are limited. In the last decade, new insights into the underlying molecular mechanisms of ET and PV have shown their growing clinical relevance and have led to the guidelines published by the World Health Organization (WHO).3,4 which have replaced those of the Polycythemia Vera Study Group (PVSG).5 Because the clinical and hematologic findings are similar in children and adults with Ph− MPD, it has been generally accepted that specific diagnostic criteria developed for adult patients with ET and PV should also be applied to pediatric cases.3−5 Recently, our group and others have reported a low incidence of JAK2V617F mutations in ET and PV occurring in childhood.6,7 Further studies have not confirmed these findings in PV patients6; however, at least in ET, we clarified that they were due to the MPLS505A-activating mutation mimicking a true MPD.7 To avoid inappropriate invasive investigations and overtreatment in hereditary forms, we proposed that children suspected of MPD should undergo a specific diagnostic workup.9,10 In adults, management and therapeutic options are supported by controlled studies, and the clinical outcome of patients treated according to the current clinical practice is predictable.11,12 In contrast, the treatment approaches in children are highly heterogeneous and are often imported from the adult experience.3,13−15 With regard to the long-term outcome of MPD, there have been many studies on life expectancy, complications (thrombosis, myelofibrosis, and leukemia),1,16−23 thrombophilia as an additive risk factor in younger patients,24 pregnancy course in adults and young individuals,25−29 whereas few studies have been conducted in children.6,13,30

The present study was carried out in a series of 64 patients < 20 years of age at diagnosis who were investigated for suspicion of MPD according to diagnostic work-up9 with the aim of analyzing the clinical and biologic features of the different forms, the treatment strategies used, and the overall outcome, including hematologic evolution, thrombotic events, and pregnancies. Taking advantage of the prolonged period of clinical observation of this cohort of patients, we provide some suggestions for the clinical management of children and adolescents with MPD.

Methods

This retrospective study included 64 consecutive patients suspected of having MPD who were observed at the Hematology Center of the Sapienza University of Rome between December 1981 and March 2009. The study


*F.G. and L.T. contributed equally to this work.

The online version of this article contains a data supplement.

© 2012 by The American Society of Hematology
was approved by the institutional ethics committee. The inclusion criteria were a diagnosis satisfying the PVSG criteria and, from 2002 on, the WHO criteria. Secondary causes of thrombocytosis or erythrocytosis were carefully ruled out in all patients. At diagnosis, cytogenetic analysis revealed a normal karyotype in 49 of 49 tested patients and bone biopsy showed the absence of bone marrow (BM) reticulin fibrosis in 37 of 46 (80%) patients. Clinical and hematologic evaluations were planned at intervals scheduled according to the individual outcome. Since 2002, blood samples from 51 of 64 MPD patients were collected after informed consent in accordance with the Declaration of Helsinki. Cell cultures for endogenous erythroid colony (EEC) growth were performed as described previously. Clonality of hematopoiesis was examined in all female patients by the human androgen receptor assay and by human androgen receptor assay methylation-specific PCR analysis. The presence of JAK2V617F or JAK2 exon 12 mutations were investigated using the method described by Baxter et al and Scott et al, respectively. The mutated allele burden was measured according to the method of Vannuchi et al. As described previously, all patients with hereditary forms were investigated for all those mutations that were detected in hereditary cases of thrombocytosis and polycythemia. Furthermore, in all patients with unidentified genetic defects from both hereditary and sporadic groups, a broad search for several mutations associated with myeloproliferative neoplasms was carried out. Patients with erythrocytosis were generally investigated for mutations of the following genes: hypoxia-responsive element (HRE) of the human erythropoietin gene (Epo), erythropoietin receptor (EpoR), hypoxia-inducible factor-2α and -1α (HIF-2α and HIF-1α), von Hippel-Lindau (VHL), prolyl hydroxylase domain protein 1-3 (PHD1-3), STAT5, lymphocyte-specific adaptor protein (LNK), and Ten-Eleven Translocation-2 (TET2). Similarly, patients with JAK2 wild-type thrombocytosis were investigated for the following genes: 5′-untranslated region of thrombopoietin (THPO), thrombopoietin receptor (MPL), LNK, and TET2. All primers, PCR conditions, and relative references are provided in supplemental Table 1 (available on the Blood Web site; see the Supplemental Materials link at the top of the online article).

The presence of thrombophilic conditions was investigated in 40 patients. Functional protein C (PC; normal range, 70%-115%) and free protein S (PS) Ag (normal range, 64%-124%) were determined by automated latex ligand immunoassay. Functional antithrombin (normal range, 70%-115%) and free protein C were evaluated by the automated chromogenic method. Lupus anticoagulant, 75%-132%) and activated automated latex ligand immunoassay. Functional antithrombin (normal range, 70%-115%) and free protein C (normal range, 43 (53%) patients with sporadic thrombocythemia (ST), 16 (25%) with hereditary thrombocythemia (HT), 11 (17%) with sporadic polycythemia (SP), and 3 (5%) with hereditary polycythemia (HP). No familial cases of acquired ET and PV were recorded.

**Patients with ST and HT**

Clinical, hematologic, and laboratory features. The main features of patients grouped as ST or HT are shown in Table 1. Generally, patients with HT were diagnosed at a younger age than those with ST (P = .0418). Except for the significantly higher Hct value in the ST group (P = .0047), we did not find any significant difference in the other hematologic features between HT and ST. Similarly, the 2 groups were not distinguishable by BM histology, both being characterized by hypercellularity, giant megakaryocytes, and absent or low (grade 0-1/1) reticulin fibrosis. No significant differences in the clinical features were recorded in the 2 cohorts, although ST patients presented with symptoms or organomegaly at diagnosis more than those with HT. Generally, neither bleeding episodes or thrombotic events were recorded at diagnosis or as an inaugural manifestation of the disease.

Concerning the laboratory features, 10 of 21 (48%) ST patients were JAK2V617F mutated and 7 of 11 (63%) ST female patients exhibited monoclonal hemopoiesis. In contrast, all investigated patients with HT were JAK2 wild-type (P = .0049) and all HT female patients showed a polyclonal hemopoiesis (P = .0128); moreover, 15 of 16 investigated HT patients harbored the MPLS505A mutation (P < .0001 in comparison with ST). No mutations other than JAK2V617F or MPLS505A were identified in the 2 cohorts of patients. Among ST cases, no significant differences in clinical, hematologic, and biologic features were found between JAK2V617F-mutated and JAK2 wild-type patients, as shown in Table 2. In JAK2V617F-positive patients, the burden of mutated alleles ranged from 6%-50% (Table 1) and was not influenced by the administered cytoreductive treatment. In JAK2V617F-mutated and MPLS505A-negative patients, no mutations of the other investigated genes were detected (for details, see supplemental Methods).

Thrombophilic abnormalities were investigated in 31 thrombocytopenic patients. As shown in Table 3, a heterozygous F1R20210A mutation was found in 3 patients (9.5%), combined with other acquired (prolonged silica clotting time ratio in 1 case) and/or inherited (MTHFRC677T polymorphism) abnormalities in 2 patients. Moreover, a heterozygous FVL combined with a MTHFRC677T polymorphism was detected in 2 patients (6.5%).

**Treatment.** Based on the clinical features and hematologic findings, ST and HT were indistinguishable until the hereditary form was better defined. Therefore, until a few years ago, the same therapeutic approach was used for ST and HT patients, using different antiplatelet and cytoreductive agents over the years of the study, as detailed in supplemental Table 2. Overall, 10 thrombocytopenic children, especially with those HT, did not undergo any
treatment. Antiplatelet treatment, mostly acetylsalicylic acid (ASA), was started in 27 of 34 (79%) patients with ST and in 9 of 16 (56%) patients with HT at different times during the observation period. However, the use of ASA progressively decreased over the study period both in newly diagnosed patients and in those on treatment; at the last follow-up, 6 of 34 (15%) patients with ST and in 3 of 16 (19%) patients with HT were still receiving ASA (Table 1).

Cytoreductive agents, mostly hydroxyurea (HU), IFN-α, and anagrelide (ANA), were used in 25 of 50 (50%) patients for a mean time of 126 months; 15 of these patients received more than one agent. A significantly greater number of children with ST (68%) received cytoreductive therapy than those with HT (12.5%; P = .0006). Over the years, cytoreduction was stopped in 5 patients; nevertheless, at the last observation, 19 of 34 (56%) ST patients were still receiving cytoreductive agents compared to 1 of 16 (6%) children with HT (P = .0007).

**Clinical outcome.** As reported in Table 1, after a median follow-up of 128 months for ST and of 137 months for HT, 3 patients (5%) without any significant thrombophilic abnormalities experienced a thrombotic event that occurred during infectious episodes. A 25-year-old ST male developed a portal thrombosis during HU treatment 1 year after a posttraumatic splenectomy; a 21-year-old HT female had a superficial thrombophlebitis during therapy with low-dose ASA, and a 13-year-old HT male, who had previously undergone posttraumatic splenectomy, experienced a peripheral arterial occlusion while on treatment with low-dose ASA and HU.

<table>
<thead>
<tr>
<th>Demographic and hematologic characteristics</th>
<th>ST (n = 34)</th>
<th>HT (n = 16)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males/females</td>
<td>10/24</td>
<td>7/9</td>
<td>.35</td>
</tr>
<tr>
<td>Median age, y (range)</td>
<td>15 (5-19)</td>
<td>12 (3mos-17)</td>
<td>.0418</td>
</tr>
<tr>
<td>Median WBCs, ×10⁹/L (range)</td>
<td>9.88 (5.62-22.22)</td>
<td>8.43 (5.17-16.06)</td>
<td>.215</td>
</tr>
<tr>
<td>Median Hct, % (range)</td>
<td>41.65 (29-53)</td>
<td>36.15 (32.3-42)</td>
<td>.0047</td>
</tr>
<tr>
<td>Median platelets, ×10⁹/L (range)</td>
<td>1.109 (633-2.800)</td>
<td>990.5 (611-2.950)</td>
<td>.303</td>
</tr>
<tr>
<td>BM biopsy, n (%)</td>
<td>34/34 (100%)</td>
<td>5/16 (31%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypercellularity, n (%)</td>
<td>15/34 (44%)</td>
<td>1/5 (20%)</td>
<td>1.00</td>
</tr>
<tr>
<td>Giants megakaryocytes, n (%)</td>
<td>5/34 (15%)</td>
<td>0/5</td>
<td>1.00</td>
</tr>
<tr>
<td>Reticulin fibrosis 0-1/1, n (%)</td>
<td>7/34 (20.5%)</td>
<td>1/5 (20%)</td>
<td>1.00</td>
</tr>
</tbody>
</table>

**Clinical findings at first presentation**

- Symptoms, n (%): 12 (35%) for ST and 4 (25%) for HT; P = .526
- Headache: 10 for ST and 3 for HT
- Paresthesias: 2 for ST and 1 for HT; P = .702
- Splenomegaly, n (%): 6/32 (19%) for ST and 2/15 (13%) for HT; P = .472
- Hepatomegaly, n (%): 2/32 (6%) for ST and 0 for HT
- Thrombotic events, n (%): 0 for ST and 0 for HT
- Bleeding events, n (%): 0 for ST and 0 for HT

**Biologic markers**

- EEC positive, n (%): 11/19 (58%) for ST and 5/12 (42%) for HT; P = .472
- JAK2V617F, n (%): 10/21 (48%) for ST and 0/13 for HT; P = .0049
- V617F allele burden, n: 8/10 for ST and 0 for HT
- Median allele burden (range): 21% (6%-50%) for ST and 8% (10%) for HT; P = .0128
- Clonal hemopoiesis, no. of females, %: 7/11 (64%) for ST and 0/7 for HT; P = .0001
- MPL mutations, n (%): 0/15 for ST and 1/16 (6%) for HT; P = .0007

**Treatment**

- Antiplatelet drugs, n (%): 27/34 (79%) for ST and 9/16 (56%) for HT; P = .105
- Cytoreductive therapy, n (%): 23/34 (68%) for ST and 2/16 (12.5%) for HT; P = .0006
- Antiplatelet drugs at last follow-up, n (%): 1/34 (3%) for ST and 0/16 for HT
- Cytoreductive therapy at last follow-up, n (%): 19/34 (56%) for ST and 1/16 (6%) for HT
- ANA: 7/19 (37%) for ST and 4/19 (21%) for HT
- IFN-α: 7/19 (37%) for ST
- IFN-α + HU: 119 (5%) for ST

**Clinical outcome**

- Splenomegaly - reticulin fibrosis 1-2, n (%): 3/34 (9%) for ST and 0 for HT; P = .542
- Time to evolution, mo (37, 106, 119): (37, 106, 119) for ST and 0 for HT
- Thrombotic events, n (%): 1/34 (3%) for ST and 2/16 (12.5%) for HT; P = .236
- Time to thrombosis, mo (64) (28, 64): (64) for ST and (28, 64) for HT
- No. of pregnancies/no. of patients: 15/6 for ST and 6/2 for HT
- Abortions: 6 for ST and 0 for HT
- Spontaneous: 2 for ST
- Elective: 4 for ST
- Childbirths: 9/15 for ST and 3/3 for HT; P = .678
- Malignancies, n (%): 1 (3%) for ST and 1 (6%) for HT
- Splenectomy, n (%): 1 (3%) for ST and 0 for HT
- Lost to follow-up, n (%): 10 (29%) for ST and 3 (19%) for HT
- Median follow-up, mo (range): 128 (13-332) for ST and 137 (27-327) for HT

ST indicates sporadic thrombocythemia; HT, hereditary thrombocytosis; n, number of patients; EEC, endogenous erythoid colony; ANA, anagrelide; HU, hydroxyurea; and IFN-α, interferon-α.
After a median follow-up of 132 months, none of the thrombocytemic patients developed acute leukemia, whereas 2 untreated patients developed a malignancy: 1 HT male had a localized malignant melanoma and a ST female developed a renal carcinoma. A progressive spleen enlargement combined with an increase of reticulin fibrosis up to grade 1-2 was recorded in 3 of 34 (9%) ST patients (1 of whom was never treated with cytoreductive drugs), whereas no cases of overt post-ET myelofibrosis according to standard criteria were documented among our patients.

**Pregnancy.** Data on pregnancies are summarized in Table 1. During the follow-up, a total of 18 pregnancies among 6 ET and 2 HT female patients were recorded. Five of the 8 pregnant females had previously received one or more cytoreductive agents, mostly HU. At the time of conception, antiproliferative treatment, namely IFN-α (n = 1), and ANA (n = 1), was documented in 9 cases (50%) and was discontinued in all but 2 patients, who were treated with IFN-α. As antiplatelet therapy, an individualized treatment consisting of ASA alone (n = 5), ASA in combination with low-molecular-weight heparin (n = 3), or low-molecular-weight heparin alone (n = 2) was planned in 10 patients. The 18 pregnancies resulted in 12 successful live births and in 6 first-trimester abortions, 4 of them elective. The 2 first-trimester miscarriages occurred in a JAK2V617F-mutated ET patient during treatment with low-dose ASA. Except for a thrombocytosis recorded in a newborn with the inherited MPLS505A mutation from his mother, no other hematologic abnormalities or developmental defects were recorded in the progeny of either male or female thrombocytemic patients.

**Patients with SP**

**Clinical, hematologic, and laboratory features.** As shown in Table 4, 5 of the 11 SP patients (45.5%) suffered at diagnosis from symptoms attributed to polycythemia, but 1 patient only presented with peripheral neurologic signs. The Epo serum level was within the normal range in all but 1 patient. BM histology showed hypercellularity with an increased erythropoiesis and myelopoiesis of various degrees in all patients and low (grade 0-1/1-2) reticulin fibrosis in 3 cases, 2 of whom had a concomitant splenomegaly. The most striking observation was that in this series of patients, the JAK2V617F mutation was detected in only 3 patients, all of whom had EEC growth, and, in the case of females, a clonal hematopoiesis. In the 8 JAK2V617F-negative patients, neither the JAK2 exon 12 nor mutations of the other investigated genes (for details, see supplemental Methods) were detected. It is noteworthy that in all JAK2-negative patients, the diagnosis of PV was supported by the detection of a high RBC mass and by histologic criteria, and also by the presence of EEC growth in 1 patient. The diagnosis of PV was made according to PVSG or WHO 2001 criteria, respectively. Interestingly, among patients requiring periodic phlebotomies, 4 were JAK2-negative patients. After a median follow-up time of 113 months, no thrombotic or bleeding episodes were recorded and no evolution to overt myelofibrosis or leukemia occurred.
Heterozygous FV mutation as major predictors of vascular complications. Indeed, ET patients identified age older than 60 years and previous thrombotic episodes, whereas antiproliferative therapy and no thrombotic episodes were seldom performed in the others. None of the HP patients received antiplatelet therapy.

In adulthood, the diagnosis of Ph+ myeloproliferative neoplasms occurring in childhood is completely different. Indeed, the occurrence of an ET in pre-adolescents and adolescents is extremely rare, whereas PV is quite anecdotic. As a consequence, the precise diagnosis, biologic profile, and optimal treatment of these diseases in younger patients remain uncertain.

We hereby report the biologic features, clinical findings, treatment, and outcome of a large series of patients with MPD younger than 20 years at diagnosis followed at a single institution for a median time greater than 10 years. Clearly, our study has some intrinsic limitations, mostly because of the length of the enrollment period, the timing, and the different types of treatment (usually planned according to the adulthood experience) used over the years. Moreover, as a single-center study, genetic aspects cannot be generalized for the presence in our country of some clusters of HT or polycythemia. Nonetheless, the large amount of data collected and the very long follow-up period allowed us to highlight some important differences between MPDs occurring in adulthood and those occurring in childhood. At first look, the majority of our pediatric patients (67%) were asymptomatic, mainly those with the hereditary forms being diagnosed through a careful history of previously identified family members. However, the use of antiplatelet therapy is recommended in all PV and ET patients (except for those with very severe thrombocytosis), whereas antiproliferative therapy should be given only to patients with a high vascular risk for age or previous history of thrombosis. Moreover, in PV patients, even though specific evidences are still lacking, it is widely accepted that the Hct value should be maintained below 45%.

The scenario of Ph+ myeloproliferative neoplasms occurring in childhood is completely different. Indeed, the occurrence of an ET in pre-adolescents and adolescents is extremely rare, whereas PV is quite anecdotic. As a consequence, the precise diagnosis, biologic profile, and optimal treatment of these diseases in younger patients remain uncertain.

We hereby report the biologic features, clinical findings, treatment, and outcome of a large series of patients with MPD younger than 20 years at diagnosis followed at a single institution for a median time greater than 10 years. Clearly, our study has some intrinsic limitations, mostly because of the length of the enrollment period, the timing, and the different types of treatment (usually planned according to the adulthood experience) used over the years. Moreover, as a single-center study, genetic aspects cannot be generalized for the presence in our country of some clusters of HT or polycythemia. Nonetheless, the large amount of data collected and the very long follow-up period allowed us to highlight some important differences between MPDs occurring in adulthood and those occurring in childhood. At first look, the majority of our pediatric patients (67%) were asymptomatic, mainly those with the hereditary forms being diagnosed through a careful history of previously identified family members. However,
from the diagnostic point of view, the first remarkable observation is that a proportion of children suspected of having MPD actually suffer from a hereditary form of thrombocythemia or polycythemia, which are clinically indistinguishable from the sporadic forms in the absence of specific genetic tests. However, it is notable that patients with hereditary forms were often preadolescents or even babies (in HT) and that symptoms were reported less frequently. In our series, with the exception of 1 child, all children belonging to 4 of 5 investigated families exhibited the MPL5505K mutation when tested for HT. The clustering of this autosomal-dominant alteration in our cohort of patients has been demonstrated to be due to a common founder ancestor approximately 23 generations ago.41

An important diagnostic challenge is represented by the high prevalence of JAK2 wild-type patients among children suspected of having PV. The very low detection of JAK2-mutated patients in our SP series confirms that this diagnosis is extremely rare and unlikely in childhood; however, it also raises the problem of the actual nature of these cases of “idiopathic polycythemia” presenting with normal levels of serum Epo. Our investigations for an underlying acquired or hereditary genetic abnormality (including members of the O2-sensing pathway) in these patients was fruitless and highlighted the complexity of the regulation of erythropoiesis homeostasis. The majority of our polycythemic patients required treatment with phlebotomy. Furthermore, during the follow-up, 2 of 3 JAK2-mutated patients needed additional cytoreductive therapy to reduce concomitant hepatosplenomegaly and/or to achieve the Hct target. Biologic markers in our population are very different from those reported by Cario et al in polycythemic children, all of whom were JAK2 mutated.8 We have no explanation for this difference, although it could be hypothesized that other unknown genetic defects may underlie the JAK2 wild-type forms in our cohort of polycythemic patients. Conversely, the frequency of the JAK2V617F mutation and clonality in our ST patients was similar to that reported in adults with ET.9,16,17 Recently, several studies have reported that the JAK2 mutational status in adults characterizes 2 populations of ET patients, identifying a subgroup with characteristics similar to those of subjects affected by PV.24,43,44 On the contrary, we did not find significant differences in clinical and hematologic characteristics at diagnosis, treatment, or disease outcome between JAK2V617F-mutated and JAK2 wild-type childhood ST patients.

The final consideration on the laboratory findings in our MPD population concerns the BM histology, because in the last decade, histologic features have emerged as diagnostic parameters for ET, PV, and primary myelofibrosis.3,4 Most BM biopsies from thrombocytopenic patients revealed a marked hypercellularity, a finding more reminiscent of PV or prefibrotic myelofibrosis than of true ET. Nonetheless, after 3 decades of observation, none of our ET patients has shown a progression to an overt PV or to myelofibrosis.24,43,44 Moreover, a substantial number of adult patients experience vasomotor disturbances, mostly itching in PV cases. Currently, risk factors for thrombosis are considered to be age more than 60 years and a history of previous thrombosis,1,16-21 whereas the relationship between thrombosis and leukocytosis and/or JAK2V617F mutation24,43,49 needs prospective trials to be validated into a prognostic scoring system. The incidence of thrombotic complications (5%) observed in our population during the follow-up time was lower than that reported by other authors.18,21,45-47

The choice of cytotoxic drug has been agreed upon to avoid the risks due to prolonged exposure to myelosuppressive agents; therefore, pipobroman has been replaced by HU and, currently, IFN-α and ANA are used. It should be stressed that discontinuing a treatment that has proven safe and effective has sometimes been an arduous challenge for both the patients and their parents.

In our experience, the most important difference between adult and childhood MPD was observed with regard to clinical outcome, especially vascular events. No patient from our series experienced previous or inaugural thrombosis. In contrast, more than one-third of adult PV patients and more than one-fifth of adult ET patients suffer from an artery or venous thrombosis at diagnosis, and the risk of thrombosis exceeds 20% thereafter in both diseases.1,16-21 Moreover, a substantial number of adult patients experience vasomotor disturbances, mostly itching in PV cases. Currently, risk factors for thrombosis are considered to be age more than 60 years and a history of previous thrombosis,5,1 whereas the relationship between thrombosis and leukocytosis and/or JAK2V617F mutation24,43,49 needs prospective trials to be validated into a prognostic scoring system. The incidence of thrombotic complications (5%) observed in our population during the follow-up time was lower
than that reported in adults with MPDs,1,16-21 and was not influenced by JAK2 mutational status or by thrombophilic abnormalities, because none of the patients with hereditary or acquired thrombophilia experienced thrombosis. In contrast, leukocytosis could have an important role in predisposing young patients to thrombosis: in this respect, it is noteworthy that all 3 thrombotic events occurred in the context of an infectious episode combined with leukocytosis. Our findings suggest that the integrity of the vascular tree, typical of young individuals, plays a major role in protecting these patients from thrombosis, whereas it is overcome when additional risk factors, such as flow reduction, surgery, infection, and leukocytosis, occur. In addition, 2 of 3 patients who developed a thrombosis had a simultaneous thrombocytosis because of a MPLS505A mutation, confirming that this mutation highly predisposes to thrombosis.30

The outcome of pregnancies in our female thrombocythemic population do not differ from that reported in the general population. Indeed, if the elective abortions are excluded, the overall first-trimester miscarriage rate (14%) in our cohort was similar to that estimated in the general population50 and lower than that reported in female ET patients (21%-35%) in a larger series.25-29 The lower rate of spontaneous abortions observed in our study is probably because of the tailored therapeutic interventions performed in the planned pregnancies, when the type of antithrombotic prophylaxis was chosen according to the different thrombophilic risk factors. In addition, the spontaneous decrease of the platelet count during pregnancy, reported as a common finding in pregnant women with ET,25,26 occurred in most of our pregnancies, so that a cytoduction with IFN-α was necessary in only 2 patients.

Finally, in our cohort of patients with a median follow-up greater than 10 years, a progressive increase of spleen size was documented in 8% of patients, but none has so far evolved into an overt myelofibrosis. The absence of gradual splenomegaly and/or BM fibrosis detected in our familial forms does not contradict data reported previously in a large series of HT patients older than those included in the present study.30 Indeed, the detection of splenomegaly and the progression toward a significant BM fibrosis in MPLS505A-mutated patients seemed to be age dependent and related to disease duration. Moreover, in our population, the prolonged exposure to different myelosuppressive agents did not affect the risk of developing second solid cancers.

Our experience suggests that in children suspected of having MPD, the possibility of an inherited form should be considered. Further, in thrombocythemic children, genetic tests on peripheral blood are helpful to avoid the use of invasive procedures in the familial form. It is difficult to derive definite indications on how to treat young patients with MPD on the basis of data collected over a long time period because they do not exist. Nevertheless, for treatment planning, it is important that disorders capable of exacerbating thrombocytosis, such iron deficiency and/or inflammatory status, are not underestimated. It should also be considered that MPD in children has a very favorable course, with some inherited thrombocytosis conferring a thrombotic risk in adults greater than that of true ET.30 The current therapeutic approach followed at our

---

**Figure 1. Therapeutic algorithm for thrombocythemic and polycythemic children.** The graphics in the lowest section show the number of patients undergoing the different therapeutic options: white sections refer to all asymptomatic patients, the gray sections indicate all symptomatic patients, and the darkest sections are indicative of all symptomatic patients resistant to low-dose ASA and/or with uncontrolled myeloproliferation. As a rule, any treatment, including low-dose ASA, is avoided in infants whatever the platelet number.
institution is illustrated in Figure 1. In both ST and HT patients, low-dose ASA is given electively to symptomatic patients and is carefully avoided in babies, whatever the platelet number. The use of antiproliferative drugs in thrombocytopenic patients is strictly reserved to patients with vascular symptoms (often microcirculatory disturbances) resistant to ASA or to those with progressive marked organomegaly. The drug of choice as a first-line cytoreductive treatment is considered to be IFN-α; unfortunately, patients are poorly compliant with this drug and therefore ANA also could be used safely and successfully in these patients. Even though JAK2V617F-mutated PV is an anecdotal diagnosis in infancy, phlebotomy remains the mainstay of therapy for children with polycythemia, probably with a less-stringent Hct reduction than in adults (Hct levels up to 48% might be acceptable). Only polycythemic patients with progressive marked liver and/or spleen enlargement with or without symptoms resistant to ASA are candidates for cytoreductive therapy. We strongly advise against chemotherapy use in the absence of a proven clonal proliferation. Finally, we recommend a thrombophilic screening in MPD women of childbearing age to plan tailored treatment during pregnancy.

In summary, the relative absence of symptoms and the lower incidence of thrombosis compared with adults suggest that children with MPD can be managed in a more conservative manner than adults. A longer observation period will confirm whether this favorable course varies after the fourth decade of life and will enable us to define the lifetime risk for evolution to acute leukemia or myelofibrosis of MPD occurring in infancy. International cooperative studies are necessary to elucidate the molecular etiology of pediatric patients with MPD and to standardize the therapeutic approaches for the different forms.

References

Thrombocythemia and polycythemia in patients younger than 20 years at diagnosis: clinical and biologic features, treatment, and long-term outcome

Fiorina Giona, Luciana Teofili, Maria Luisa Moleti, Maurizio Martini, Giovanna Palumbo, Angela Amendola, Maria Gabriella Mazzuconi, Anna Maria Testi, Patrizia Pignoloni, Sonia Maria Orlando, Sara Capodimonti, Mauro Nanni, Giuseppe Leone, Luigi Maria Larocca and Robin Foà