Polycythemia Vera era 1939-1998 from Berkeley to Rotterdam and Change of PVSG into ECP Criteria of Myeloproliferative Disorders ET, PV and PMGM: Proceedings of the First Rotterdam MPD Workshop 1998 and Beyond

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Abstract

The PVSG defined in 1975 the myeloproliferative disorders (MPD) essential thrombocytosis (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) or agnogenic myeloid metaplasia (AMM) are three distinct disease entities with regard to clinical manifestations, natural history and outcome in terms of life expectancy. The European Clinical and Pathological (ECP) criteria demonstrated that fibroblast proliferation in PVSG defined PMF and post-ET and post-PV myelofibrosis is polyclonal indicating that myelofibrosis (MF) is secondary in all variants of myeloproliferative syndromes. By including bone marrow histopathology the ECP defined between 1998 and 2000 the prefibrotic MPDs ET, PV and primary megakaryocytic granulocytic myeloproliferation (PMGM) are three distinct myeloproliferative disease (MPD) entities. Clinical, hematological and morphological characteristics, in particular megakaryocytopenia and bone marrow cellularity, reveal diagnostic features, which enable a clear-cut distinction between two prefibrotic MPDs ET and PV versus PMGM as the third distinct MPD entity. Life expectancy is normal in normocellular ET, normal during the first ten years and compromised during the second ten years follow-up in PV, but shortened in the prefibrotic hypercellular stage of PMGM. First line treatment options anno 2000 were control of platelet function with low-dose aspirin in ET, low-dose aspirin on top of phlebotomy in PV and a wait and see strategy in the prefibrotic and fibrotic stages of PMGM. Pegylated Interferon (IFN) was proposed in between 1998 and 2000 as the first line non-leukemogenic treatment option in prodromal PV and early or classical stages of PV. Because of its leukemogenicity hydroxyurea should be postponed as long as possible and to be used in progressed MPD restricted to the hypercellular stages of PV and ET for the treatment of uncontrolled thrombocytosis, leukocytosis splenomegaly and constitutional symptoms. These conclusions could be confirmed in the Dutch updates since 2000, are still valid and did not change significantly between 2008 and 2018 due the discovery of JAK2, CALR and MPL driver causes of MPN between 2005 and 2013.

Keywords: Megakaryopoiesis; Erythropoiesis; Granulopoiesis; Myeloproliferative disorders (MPD) essential thrombocytemia; Polycythemia vera; Agnogenic myeloid (megakaryocytic/granulocytic) metaplasia (AMM)

Introduction

The first Rotterdam Workshop on Myeloproliferative Disorders (MPD) 1998 was organized by Jan Jacques Michiels and Juergen Thiele and started with the first International Scientific State of the Art Session of the International PVSG chaired by Jan Jacques Michiels. Dr. Michiels highly welcomed Dr. Nathaniel Berlin as invited honorary guest to represent the PVSG and to introduce the PVSG concept of polycythemia vera (PV) for the members of the European Working Group on MPD (EWG.MPD) of the European Hematology Association (EHA).

Dr. Nathaniel Berlin joined and opened the “First Scientific Meeting of the International PVSG” held on March 4, 1998, Thursday evening from 1800 to 2000 hours at Novotel, Rotterdam. The program was organized by Dr. Michiels reflecting the current activities of the International PVSG:

1. Berlin NI: The Continuation of the International PVSG, links between the USA and Europe.
2. Fruchtmann S: Rationale for the use of Hydroxyurea and supplemental phlebotomies in PV.
4. Thiele J and Kvasnicka HM: Bone marrow histopathology as a specific clue to ET, PV and PMGM.
6. Michiels JJ: Changing insights in the natural history, diagnosis and treatment options in PV ET and PMGM.

Firstly, I want to thank Dr. Michiels for inviting me to this meeting and for asking me to open the First Business meeting of the International PVSG 1998. I am delighted to be here to see friends of long standing. Richard Silver, who left the National Cancer Institute just before I got there and Yves Naeije who in the middle 1960s came to the NIH with the late Catherine Dresch, to discuss erythrokinesins and Steven Fruchtman who maintains the PVSG data. And last it is great pleasure to meet and get know those of you who have been until today names...
on papers. I am particular pleased to see the leaders of the French and Italian Polycythemia Vera study Groups here, I would not dare to try to pronounce the groups names in French or Italian that courtesy if nothing else requires. Turning now to the two themes I wish to present today (March 13, 1998), the first is a brief history more personal, the second a glimpse into what I believe this group can do or perhaps what I would like to see it do. My association with the polycythemias began in June 1947 at the Donner Laboratory of the University of California as a graduate student of John Lawrence and at the same time began my lifelong friendship with Louis Wasserman who was working at the laboratory that summer (Figure 1). The modern era in the understanding and treatment of PV began in 1939 when Lawrence treated the first patient with P32 [1]. The results in the first two patients were reported in 1940. Each had an excellent response; in fact one of these patients was alive when we published our review in 1953 in Medicine [2]. Today one can say it was not necessary to demonstrate the effectiveness of P32 in more patients. These two patients are in themselves sufficient. It was at the Donner Laboratory that Wasserman began the measurement of arterial oxygen saturation as a diagnostic tool where Huff initiated the studies on kinetics of erythropoiesis with radioactive iron and I began the use of blood volume measurements with P32 labeled red cells in diagnosis and management [3-5]. It was from the patients treated at the Donner Laboratory that we were able to report in 1953 for the first time the life expectancy in P32 treated patients (2) and probable had the data to show that it approached normal, although it was not until 1991 that Rozman showed that this was so in Spanish patients [6]. This has been confirmed by Najean in French patients and by the Italian group in Italian patients [7,8].

Wasserman favoured the concept that PV is a neoplastic process of the whole bone marrow and proposed a hypothetical concept of the course of PV (Table 1 and Figure 2) [9].

Wasserman distinguished at least five subsequent stages in the natural history of PV.

Stage 1

Pure erythrocytemia due to myeloproliferative disease with increased haemoglobin, hematocrit and red cell mass, normal leukocyte and platelet counts, and no splenomegaly on palpation.

Comparable incidence of Acute Leukemia by Protocol and Treatment in the Phlebotomy arm of PVSG 01 and HU PVSG 08 according to Fruchtmann

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Protocol</th>
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<th>Total Events</th>
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<td>first 765 weeks of study</td>
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<td>51</td>
<td>3</td>
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<td>Phleb 01</td>
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Figure 1: Louis Wasserman, Founder of the PVSG. Photo courtesy of Nathaniel I. Berlin at the occasion of his active participation at the First Rotterdam Workshop on Myeloproliferative Disorders (MPD) of the European Working Group on Myeloproliferative Disorders: EWG.MPD in Rotterdam, March 1998.

Figure 2: The concept of Wasserman on the course of polycythemia vera of the fibroblasts[1995][9]. In PV, the hyperplastic marrow is a neoplastic pannerythopoiesis that expands to encompass the total marrow space at the expense of the fat cells. Blood examination reveals an erythrocytosis and usually a granulocytic leucytosis, thrombocytosis, and immature red and white cells. With continued hyperactivity, the dominant extra-osseous potential marrow becomes functionally active and the site of extramedullary hematopoiesis (stage of myeloid metaplasia) as the spleen and liver enlarge. The bone marrow shows diminution in erythropoiesis and secondary proliferation. With time progressive changes in cellular composition of the marrow occur in early spent phase PV. Fibroblastic or osteoblastic proliferation may encroach on hematopoietic cell activity with reduction of erythropoiesis. Progressive dysmature megakaryocytic fibroblastic proliferation and progressive splenomegaly is the hallmark of advanced myeloid metaplasia associated with anemia and a leukoerythroblastic blood picture. Spent phase PV, pronounced splenomegaly, myelofibrosis and acute leukemia are all depicted as stemming from a common stage of myeloid metaplasia in the bone marrow and extramedullary metaplasia in the spleen and liver.

Stage 2

The polycythemic stage (prefibrotic)

Stage 3

Progressive myeloid metaplasia with different grades of reticulin and collagen fibrosis in the bone marrow, and progressive splenomegaly in about one third of the cases during long-term follow-up. The polycythemic stage and subsequent transformation into progressive myeloblastic myeloid transformation may elapse from 5 to 25 years.
Stage 4

Spent phase PV reflects a period of normal red cell values (so-called spontaneous remission of PV) with large spleen enlarged liver, pronounced thrombocytosis is frequent with bizarre giant platelets and granulocytic leukocytosis.

Stage 5

Post-PV myeloid metaplasia, myelofibrosis (dry tap on aspiration) with various degrees of leukoerythroblastosis, anemia and pronounced splenomegaly (Figure 2) [9].

The PVSG was created in 1967 as a multi-institutional multi-national cooperative with Wasserman as its Chairman and the Central Office at Mt Sinai. I served for a time as the vice-chairman until Paul Berk joined the staff of Mt Sinai. The PVSG developed the diagnostic criteria that are widely used and cited [10]. There are more than 280 citations in the literature, certainly some are self-citations, we developed an algorithm for the evaluation of an elevated hematocrit [10,11], initially we called it a decision tree and we developed and carried out what has become known as PVSG 01-protocol – our first randomized study comparing P², chlorambucil and phlebotomy and we developed recommendations for treatment [12]. We have published reports from the PVSG in 1976, 1987 and 1997 in Seminars in Hematology and in 1995 published our book Polycythemia Vera and the Myeloproliferative Disorders edited by Wasserman, Berk and Berlin [9,13-16]. We did not do a systematic review of symptom relief, nor changes in spleen or liver size or blood pressure. That was done at Berkeley in much smaller group of P32 treated by Wasserman, Berk and Berlin [9,13-16]. We did not do a systematic review of symptom relief, nor changes in spleen or liver size or blood pressure. That was done at Berkeley in much smaller group of P32 treated patients [9]. We did both on study and off study analyses of events in the NEJM paper on chlorambucil [12] but subsequently all our efforts of the PVSG 01 protocol are for survival on study but did comment that all event analyses were done and did not change the conclusions. We did comment on differences in the rate of withdrawal alive from study was the highest in the phlebotomy treated patients, which is mentioned in the NEJM paper on chlorambucil [12].

Today we know that life expectancy in hydroxyurea treated and PVSG defined PV patients’ approaches normal but questions remain. The two recent papers in Blood by Najean and Rain are important [7,17]. They raise major questions about how best to treat initially. I will not attempt to discuss treatment options of the later phases except that we did a study of the treatment of the acute leukemia phase—it was not successful and we discussed extensively and in fact wrote a protocol for the treatment of the splenomegalic myeloproliferative phase that proved to be difficult to carry out. The Najean paper in the November 1, 1997 issue of Blood provides additional data to answer the question is hydroxyurea a leukemogen, which I think it is [17].

Today anno 1998 the questions, which I pose are:

1. Shall we revise the PVSG diagnostic criteria as Dr. Pearson [18] and our host Dr. Michiels have suggested [19]?
2. How shall blood volume measurements be reported, as ml/kg or as some function of body composition?
3. How shall they be interpreted, namely when is the line crossed that they are diagnostic?
4. When are they necessary (desirable) either initially or during the course of management?
5. Can we as a group state that hydroxyurea is leukemogenic?

In the process of developing treatment guidelines what criteria should be used in the decision making process, what is best for the patient in terms of life expectancy and what produces the greatest symptomatic relief, what is the simplest for the treating physician and does not compromise the outcome, which requires the least compliance by the patient as has been suggested by Najean and others but Dick Silver will make the case for interferon [20].

Last we must all acknowledge that the molecular biology era is here. I do not know where it will lead. It has already given us the finding that PV is a clonal disorder which Lawrence and I discussed in the early 1950’s in terms, is it a neoplasm. In closing I wish to pay tribute to the French and Italian Groups and their leaders Najean and Barbui. They have moved the leadership in the study of PV from the USA (Spivak & Silver) to Western Europe. I look forward to the ECLAP study to answer the question can aspirin lower the hemorrhagic and thrombotic complications [21]. As I read and re-read some of the recent literature [22-41], I must say that I do not come before you today with original ideas of what should be done. I can only add my choice to that of others and last for the sin of omission in failing to recognize many of the contributions of those here today I apologize and ask forgiveness and for not mentioning only the senior authors in this talk I apologize.

Controversies in the Management of MPDs: What is the Progress since the Demise of the PVSG in 1997 (Fruchtmann SM)

As far as I can derive from the issue in Seminars in Hematology in January 1997 [42], there is no residual activity of the PVSG and all PVSG protocols are closed many years ago [11,43]. We have discussed and learned much from the results of the PVSG studies at the various meetings of the EWG.MPD since 1994 summarized in The Chronic Myeloproliferative Disorders (CMPD): Essential Thrombocytocemia, Polycythemia Vera and Megakaryocytic Myeloid Metaplasia. Leukemia & Lymphoma volume 1996 Guest Edited by Jan Jacques Michiels [19]. From these publications, we got the very strong feeling to refrain from all old PVSG studies including the old studies of Najean from Paris, which all are extensively reviewed in the Leukemia & Lymphoma issue of 1996 [35]. The main conclusion from the PVSG is that Hydroxyurea (HU) is currently recommended as the least leukemogenic approach and supplement to aspirin/phlebotomy for newly diagnosed patients, who are at risk for thrombosis and for PV patients with progressed myeloproliferative disease at presentation or during follow-up. The landmark studies of Najean in Blood stresses the toxicity of long-term HU treatment in PV [44,45]. In view of the available data of Silver on interferon in PV, we now have to address the question how to design a worldwide acceptable study protocol in PV [46]. How should such a study design in PV look like to address the key question not to undertreat or over treat PV patients during the very long-term follow-up of 10, 20, and even more than 30 years. How to organize and to fund such long-term PV-studies, the very large retrospective Italian study of more than 1200 PV-patients in the Annals of Internal Medicine heavily treated and followed up between 1975 and 1995 does not provide us the relevant information in offering tools for the best treatment modality in PV [8]. Michiels reviewed The Myeloproliferative Disorders ET, PV and megakaryocytic myeloid metaplasia in 1996 [23]. Michiels, Barbui and Finazzi described the vascular complications in patients with PV in Seminars in Thrombosis 1997 from the standpoint of the least toxic approach by experienced and sensitive doctors from the literature [47,48]. Since the first annual meeting of the European Hematology Association (EHA) in 1994, Michiels founded and organized the annual Scientific Working Group (SWG) on Myeloproliferative Disorders...
agents patients were randomized to influence long term prognosis and into trials and work collaboratively and established that pharmaceutical were required to accrue sufficient numbers of patients to be entered diseases to be studied and that multi-institutional, international trials groundwork for establishing clinical criteria for the ET, PV and PMF Thiele, Barbui, Landolfi and Michiels. Clearly, the PVSG defined the leadership of the innovative clinical investigators Pearson, Georgii, due to the loss of no funding, leadership in design and performance agents commonly used in that era [49,50]. Since the demise of the PVSG clinical trials and determine the optimal treatment strategy with the and to establish criteria for the diagnosis of MPDs enter patients onto ERBBMH4CT961433) and started in 1997.

The major goals of the PVSG was to search for the least toxic approach and to establish criteria for the diagnosis of MPDs enter patients onto clinical trials and determine the optimal treatment strategy with the agents commonly used in that era [49,50]. Since the demise of the PVSG due to the loss of no funding, leadership in design and performance of pivotal clinical trials in MPDs has shifted to Europe, under the leadership of the innovative clinical investigators Pearson, Georgii, Thiele, Barbui, Landolfi and Michiels. Clearly, the PVSG defined the ground work for establishing clinical criteria for the ET, PV and PMF diseases to be studied and that multi-institutional, international trials were required to accrue sufficient numbers of patients to be entered into trials and work collaboratively and established that pharmaceutical agents patients were randomized to influence long term prognosis and transformation to acute leukemia. The use of clinical criteria to establish diagnosis was extremely important in establishing similar cohorts of patients to be entered onto trials, but it lead to confusion amongst the practicing community that concluded that unless the criteria were met, a patient could not carry the diagnosis. It required an educational effort to instruct physicians that this was a misconception.

The notion of multi-institutional, international, prospective trials was unique at that time, but clearly the PVSG established the frame work and communicative infrastructure to create a creative and successful working environment. The PVSG O1 trial set to rest the notion that all patients needed cytoreductive therapy, due to the observation of increased acute leukemia occurring in patients so treated. Unfortunately patients treated with phlebotomy alone had a higher rate of thrombotic complications, with many of these thrombosis causing death. Thus, the PVSG established that thrombosis and acute leukemia were the major causes of morbidity and mortality in Ph-MPDs. In order to establish a cytoreductive regimen that was safe for long term use, the PVSG studied hydroxyurea to address the controversial question whether or not hydroxyurea is leukemogenic.

The PVSG data and other investigators report that the incidence of leukemic transformation in hydroxyurea treated patients in the PVSG 08 (Table 2) [42,43] is higher than presented in the phlebotomy arm of the PVSG 01 study. Such studies must report other therapies the patient received, due to the observation by both Najean [44,45] and Murphy [50] that an extremely leukemogenic formula is when one cytoreductive therapy especially alkylators is followed by hydroxyurea. More recently, anagrelide has been investigated in a series of abstracts presented at the American Society of Hematology (ASH 1997). We have reported on its efficacy in preventing both thrombosis and hemorrhage in these patients, and recently Tefferi et al published on its long term safety of anagrelide in ET regarding safety, efficacy and absence of leukemogenicity [46].

**Erythromelalgic Thrombotic Thrombocythemia in ET and PV (Michiels JJ, Van Vliet HHDM and Van Genderen PJJ)**

Michiels discovered between 1973 and 1985 that aspirin responsive erythromelalgia and its ischemic complications and aspirin responsive migraine-like atypical transient ischemic cerebral ocular (MIAs) as well as coronary ischemic attacks are specific clinical manifestations of thrombocythemia vera caused by platelet-mediated arteriolar inflammation and thrombosis in ET at platelet count above 400 × 10^9/L and in PV patients associated with thrombocythemia at platelet count above 350×10^9/L [27,48,49]. Michiels and Ten Kate recognized diagnosis was extremely important in establishing similar cohorts of patients to be entered onto trials, but it lead to confusion amongst the practicing community that concluded that unless the criteria were met, a patient could not carry the diagnosis. It required an educational effort to instruct physicians that this was a misconception.

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that erythromelalgic thrombotic thrombocythemia (ETT) in ET and PV patients (Figures 4 and 5) had overlapping bone histology features (Figure 6). Bone marrow histology in ET is featured by normocellular increase of large mature megakaryocytes (M) or shows a hypercellular myeloproliferation of increased erythropoiesis and clustered mature megakaryocytes (prodromal PV). Bone marrow histology in PV is featured by increased erythropoiesis and clustered mature large megakaryocyte proliferation (EM) in early stage classical PV but increase of trilinear erythro-megakary-granulocytic (EMG) myeloproliferation in hypercellular PV. The morphology and clustering of large mature and pleomorphic megakaryocytes are identical in ET, prodromal PV and early stage PV in both ET and PV who presented with ETT (Figure 6). Michiels Ten Kate and van Vliet recognized ETT in ET and PV are very likely caused by hypersensitive thrombocythemia platelets, which spontaneously activate at high shear in the endarterial circulation and secrete their products thus forming aggregates that transiently plug the microcirculation or result in occlusive platelet thrombi in arterioles or small arteries (Figure 4) [48,49]. Michiels et al. [49] produced clear evidence that erythromelalgia and MIAs in ET and PV patients are relieved (cured) by treatment with aspirin and by reduction of platelet count to normal (<350 × 10^9/L), but not by coumadin and the platelet ADP receptor inhibitor ticlopidin (Figure 5). In patients with thrombocythemia associated with PV, increased hematocrit and whole blood viscosity related to increased interactions of hypersensitive platelets, activated granulocytes (increased LAP score and erythrocytes) severely aggravate the platelet-mediated microvascular ischemic circulation disturbances into major arterial and venous thrombotic complications (Figure 5) [19,22].
and venous thrombosis, but fails to prevent the platelet-mediated microvascular circulation disturbances because thrombocytopenia in PV in remission by phlebotomy alone persisted [18,50]. Michiels et al demonstrated in the 1980s and 1990s that complete relief and prevention of erythromelalgia, atypical microvascular migraine-like transient neurologic and ocular manifestation in ET patients and major thrombosis in PV patients are obtained by treatment with low dose aspirin on top of correction of the hematocrit to 0.40 by phlebotomy, or by treatment with the platelet lowering agents anagrelide or interferon in ET or by reduction of increased platelet and leukocytes by interferon or hydroxyurea in PV in remission by phlebotomy (Figure 5) [20,28,30,48,50,51,52-56].

Van Genderen et al. [55] demonstrated in the 1990s that symptomatic thrombocytopenia (ET and PV) patients with erythromelalgic circulation disturbances have shortened platelet survival, increased platelet activation markers beta-thromboglobulin (beta-TG), platelet factor 4 (PF4), increased endothelial cell markers thrombomodulin (TM), and increased urinary thromboxane B2 (TXB2) excretion indicating platelet-mediated processes in vivo [52,53]. Inhibition of platelet cyclooxygenase (COX1) by aspirin treatment of thrombocytopenia patients complicated by erythromelalgia resulted in the disappearance of erythromelalgic circulation disturbances, correction of shortened platelet survival, and return of plasma levels Beta-TG, PF4, TM and TXB2 excretion to normal [50,52,53]. The Van Genderen studies extended the observations of Michiels and Van Vliet by the demonstration that erythromelalgia and MIAs in ET are characterized by platelet activation and endothelial cell damage but not by thrombin generation, thereby giving a plausible explanation for the inefficacy of coumadin derivatives and heparin in the prevention and treatment of erythromelalgia and MIAs in ET. Histopathology and immunochemical analysis by Van Genderen of skin punch biopsies derived from erythromelalgic skin areas of 2 ET patients showed that erythromelalgic thrombi stained positively with von Willebrand factor (VWF) opposed to a weak fibrin staining [52]. These data produced by Van Genderen that erythromelalgia and MIAs in ET and PV in remission by phlebotomy are caused by platelet-VWF mediated intravascular activation and aggregation of hypersensitive thrombocytopenic platelets with subsequent sludging or occlusion by VWF-rich platelet thrombi in the acral, cerebral or coronary microvasculature [23,52].

First-line Treatment for PV with Interferon-alpha (Silver RT and Michiels JJ)

Dr Silver [21] reported on effects of long-term treatment with interferon-alpha for polycythemia vera [38,57]. The most simple and effective treatment option is based on the initial reduction of red blood cells, especially for the elderly is associated with early frequent fatal thrombosis when not on aspirin. Phlebotomy does not diminish the risk of developing myelofibrosis (MF). It has only relatively recently appreciated that hydroxyurea (HU, the standard myelosuppressive drug for PV) is associated with approximately 10% incidence of acute leukemia after long-term follow-up of about 10 years. Additional limitations of using HU in PV include, but are not restricted to, the failure to control constitutional symptoms and toxicity of HU. A review of more than 1200 patients who had PV indicated that the death rate in those receiving P5+, alkylating agents or non-alkylating myelosuppressive agents was three to four times higher than those who did not [54]. An increased risk for cancer was observed approximately 6 years after diagnosis of PV suggesting an overall unfavorable effect of myelosuppression.

Silver and Michiels proposed in 1998 to treat PV patients according to the least toxic approach with low dose aspirin and phlebotomy alone in early stage PV and to postpone potential leukemogenic agent hydroxyurea in the intermediate stage of as long as possible by using recombinant interferon (IFN) in the prefibrotic stages of PV [57,58]. If non responsive to IFN or serious side effects there is a clear indication to suppress advanced MPD disease in PV by hydroxyurea. IFN has activities against platelet derived growth factor (PDGF), transforming growth factor beta (TGF-beta). TGF-beta has powerful angiogenic properties. How TGF-beta, PDGF and cytokines interact to cause marrow fibrosis is unknown: what is of importance is that IFN therapy influences TGF-beta values to return to normal levels together with correction of increased platelet counts and spleen size in PV in responsive cases that suggest that IFN has a unique role in the treatment of the MPDs, particularly PV, and may be the first drug which may alter the natural history of the disease PV. Silver stated in 1998 that IFN represents the therapeutic evolution of the PVSG in searching for the best treatment of PV patients. The rational for using IFN-alpha in the treatment of early and intermediate prefibrotic stage of PV according to Silver includes:

1. Abatement of constitutional symptoms including itching
2. Maintenance of hemoglobin, hematocrit, leukocyte in the normal range and platelet suppression.
3. Avoidance of phlebotomy, secondary iron deficiency anemia and secondary macrocytosis associated with hydroxyurea
4. Lacks of mutagenicity.
5. Prevents or delays the development of post-PV splenic myeloid metaplasia and myelofibrosis by reduction of MPD disease burden (reduction splenomegaly).
6. Effectiveness/toxicity (risk/reward) ratio is positive.
7. Because recombinant IFN-alpha is suppressive, not curative, long-term treatment is required with careful attention to the short- and long-term nonhematopoietic effects of IFN-alpha.
8. Additional phlebotomy may be required to maintain the hematocrit in the desired target.
9. For those younger patients who will not accept IFN, phlebotomy plus antiplatelet agent anagrelide may be considered [58].
10. For elderly patients (older than 70 years) hydroxyurea should be considered for treatment.

Clear indications for the start of hydroxyurea in stage 3 PV include uncontrolled platelet count of >1,000×10^9/l during aspirin therapy; symptomatic large spleen (splenomegaly); PV-related constitutional symptoms including pruritis; leukocyte count in excess of 25 × 10^9/l (hypercellular PV); leukoerythroblastic blood picture and signs of myeloid metaplasia and major arterial or venous thrombembolic complications despite eradication of vascular risk [57,58]. The main therapeutic benefits of recombinant interferon-alpha (rIFN-alpha) therapy for PV include induction of hematological remission with elimination or reduction in the need of phlebotomy, control of thrombocytosis and leukocytosis and resolution of classical PV disease associated symptoms in particular refractory pruritis [57].

Reviews of the literature anno 1998 indicate that an overall hematological response has been achieved in more than 75% of cases within 6 to 12 months [38,58]. Doses of rIFN-alpha used to obtain hematological response...
ranged from 2 MU per week to 70 MU per week with a median dose of about 10 MU per week. Usually, dose reduction occurred in the second year of treatment [57].

The 1997-2000 Diagnostic Criteria of the MPDs ET, PV and CMGM/PMGM (Michiels JJ)

Philadelphia chromosome-positive (Ph'-ET) and chronic myeloid leukemia (Ph'-CML) constitute a separate malignant disease entity whereas ET, PV and chronic or primary megakaryocytic, granulocytic myeloproliferation (CMGM/PMGM) belong to the Ph-negative myeloproliferative disorders (MPDs) [57,58]. The megakaryocytes in Ph'-ET and CML are abnormal small with round nuclei, showing little lobulation. Both the number and size of megakaryocytes in Ph negative ET, PV and CMGM/PMGM are typically increased with loose or dense clustering of large megakaryocytes. Enlarged mature megakaryocytes with multilobulated nuclei and their tendency to cluster in a normal or slightly increased cellular bone marrow represent the hallmark of ET (Table 3 and Figure 6) [58,59]. The size and morphology of megakaryocytes are normal in reactive thrombocytosis, very small in Ph' ET and CML and enlarged in all variants of MPD. The characteristic increase and clustering of enlarged mature and pleomorphic megakaryocytes with multilobulated nuclei and proliferation of erythropoiesis in a moderate to marked hypercellular bone marrow (50 to 70%) is the diagnostic hallmark of latent, prodromal and early stage PV (Table 4 and Figure 6) [58-60]. Diagnostic bone marrow histopathology characteristics in classical PV are described by the trias of:

1. Increase of clustered pleomorphic medium sized and large mature megakaryocytes with hyperploid nuclei.
2. Increased cellularity (90 to 100%) due to trilineal erythrocyctic, megakaryocytic and granulocytic (EMG) myeloproliferation.
3. No or minor increase of fine reticulin fibers (Table 4 and Figure 6) [58-60].

In secondary polycythemia in which increased cellularity of the erythroid cell line may be present the number, size and morphology of megakaryocytes remain normal (Figure 6). The early preblastic stages stages of AMM or prePMF (Table 5, Figures 7 and 8) and fibrotic stages of AMM or PMF with anemia and large spleens without any PV features according to the PVSG appears to be a distinct dual chronic or primary megakaryocytic granulocytic myeloproliferation (CMGM/PMGM) in the Hannover Bone Marrow Classification of the MPDs [56,57]. The histopathology of the bone marrow in PMGM is dominated by atypical enlarged (larger than in ET and PV) and immature megakaryocytes with cloud-like nuclei which are not seen in Ph-ET and PV and Ph' ET and CML. (Table 5 and Figures 7 and 8) [52-57]. Myelofibrosis in ET, PV and CMGM is graded in no reticulin fibrosis (MF 0), early reticulin fibrosis (MF 1), advanced reticulin fibrosis with minor collagen fibrosis (MF 2) and advanced collagen fibrosis with or without osteosclerosis (MF 3) [25,61-65].

Bone Marrow Histopathology (Thiele J and Kvasnicka HM)

Thiele & Kvasnicka presented a systematic study on the modern approaches towards bone marrow histopathology and immunohistochemistry as a specific clue to diagnose and stage (Table 5) the myeloproliferative disorders (MPD) ET, PV and CMGM/PMGM [64], and to differentiate PMGM from ET and PV based on clinicopathological criteria (Table 5, Figures 7 and 8) [61-63]. The morphological approach attempts to assess the different subtypes of MPD by regarding their most prominent histological features like megakaryocytes and associated reticulin-collagen fibers, and myeloid or erythroid precursors. This methodology according to Michiels & Thiele will become most successful by the use of enzyme- and immunohistochemistry with a meticulous conducted analysis of megakaryo-erythro-granulopoesis and grading of reticulin and collagen fibrosis, which has to be followed by correlation of the relevant laboratory and clinical parameters for proper staging of each of the MPDs ET, PV and CMGM/PMGM (Table 5 and Figures 7 and 8). PV is not only characterized by a striking increase and clustering of pleomorphic large megakaryocytes. This clustering consists of a grouping of giant megakaryocyte together with medium-to small-sized and degenerative cell forms or naked nuclei (Figure 7). No major megakaryocyte maturation defects are observable throughout the bone marrow. As in the other subtypes of MPDs there is an obvious dislocation of megakaryocytes from the center of the bone marrow to the paratrabecular endosteal area. The number and sizes of large and mature megakaryocytes are significantly increased in ET, to large but histology fails to display maturation disturbances seen in PMGM (Table 5 and Figure 8). It should be emphasized that giant mature megakaryocytes with hyperlobulated nuclei in a normocellular bone

<table>
<thead>
<tr>
<th>Diagnostic Criteria PV</th>
<th>Confirmative Criteria PV</th>
</tr>
</thead>
<tbody>
<tr>
<td>A1</td>
<td>Raised red cell mass. RCM male&gt;36 ml/kg, Female&gt;32 ml/kg</td>
</tr>
<tr>
<td>A2</td>
<td>Absence of any cause of secondary erythrocytosis by clinical and laboratory investigations</td>
</tr>
<tr>
<td>A3</td>
<td>Histopathology of bone marrow biopsy: (a) Increase and clusters of pleomorphic enlarged megakaryocytes with hyperploid nuclei (b) Increased cellularity: pancytopenia (c) Reticulin fibres (optional)</td>
</tr>
</tbody>
</table>

Table 3: The 1980 and 1997 Rotterdam Clinical and Pathological (RCP) criteria for the diagnosis of Essential Thromocythemia proposed by Michiels & Juvonen.

Table 4: The 2000 European Clinical and Pathological (ECP) criteria for the detection of latent, prodromal, erythrocytic, classical and advanced stages of Polycythemia Vera by including bone marrow histopathology according to Michiels et al.
Platelet counts around 1000 × 10⁹/L and a hypercellular bone marrow are the hallmark of ET. PMGM usually presents with high platelet counts exceeding 400 × 10⁹/L and no known cause of reactive thrombocytosis.

No preceding or allied other subtype of myeloproliferative disorders or myelodysplastic syndrome.

Normal or elevated leucocyte alkaline phosphatase (LAP) score, normal ES, and no fever

Normal or slightly increased cellularity and no or minimal reticulin fibrosis in bone marrow biopsies.

Splenomegaly on palpation, or >11 cm on ultrasound scan or on computer tomogram (CT).

Spontaneous erythroid colony (EEC) and/or spontaneous megakaryocyte colony formation (CFU-Meg).

Platelet count in excess of 400 × 10⁹/L and no known cause of reactive thrombocytosis.

Granulocytes >10 × 10⁹/L and/or raised LAP score in the absence of fever or infection

Splenomegaly on palpation or >11 cm on ultrasound scan or CT

Spontaneous erythroid colony formation in the absence of Epo and low plasma Epo level.

A1

A2

A3

B1

B2

B3

B4

A1

A2

A3

B1

B2

B3

B4

No preceding subtype of ET PV CML or MDS

Thrombocytopenia, platelets from >400-10⁹ to high around and above 1000 × 10⁹/L

Histopathology of bone marrow biopsy: a) increase and clusters of pleomorphic megakaryocytes with hyperploid nuclei b) increased cellularity: pannymelus c) reticulin fibers (optional) 

Increase and clusters of mature giant megakaryocytes with hyperploid nuclei in bone marrow biopsies. 

Abnormal clustering and increase of atypical giant to large megakaryocytes atypical giant to large megakaryocytes and definitive maturation defects of cytoplasm and cloud-like nuclei 

Myelofibrosis MF: criteria Georgii 1998 

MF 3. advanced collagen fibrosis/osteosclerotic endophytic bone formation= advanced fibrotic

Splenomegaly normal (<12 cm) to slight increase (<15 cm) to large (>18 cm) on ultrasound scan or CT

AMM or classical PMF

D

E

A

B

C

Histopathology of bone marrow: a) increase and clusters of pleomorphic megakaryocytes with hyperploid nuclei b) increased cellularity: pannymelus c) reticulin fibers (optional) 

Definitive leuko-erythroblastic blood picture and/or tear drop erythrocytes 

Diagnostic criteria

Confirmative criteria

Table 5: European Clinical and Pathological (ECP) criteria of ET by including bone marrow histopathology according to Michiels, Georgii and Thiele for ET published in the Netherland Journal of Medicine 1999.
JAK2V617F mutated MPN disease in ET and PV patients [66,67]. A non-responsive to or side effect induced by IFN, hydroxyurea is the second line myelosuppressive treatment option in JAK2V617F mutated ET and PV patients with increased MPN-T disease burden [67]. The top 20 complaints at time of diagnosis in 399 out of 497 (81%) an MPN patient was fatigue (81%) equally high in ET, PV and MF patients [68]. Apart from fatigue about 40% to 60% of ET and PV patients presented with aspirin responsive microvascular disturbances. Itching (PV 58% vs. ET 30%) and fatigue were much more prominent in PV. About one third of MPN (ET, PV and MF) patients suffered from bone pain. MF patients suffered more frequently from constitutional symptoms of prominent fatigue and night sweats related to pronounced splenomegaly. Before the diagnosis was made in 497 MPN patients, the complaints were ascribed to other causes in 173 (35%): to stress, burned out or overstrained in 41 (24%), to depression or mystery in 14 (8%), migraine of unknown origin in 13 (8%) and to rheuma, hypertension or fibromalga in a few (Figure 9) [68].

**Outlook 2000 and Beyond**

Clinical, hematological and morphological peripheral blood and bone marrow features in particular, megakaryocyte morphology and bone marrow cellularity according to Georgii and Thiele, reveal diagnostic clues and pathognomonic features, which enables a clear-cut distinction between ET, PV and PMGM. Increase of clustered large mature megakaryocytes with mature cytoplasm in a normal or slightly increased erythropoiesis represents the hallmark of ET (Figure 6). Increase and clustering of large mature and pleiomorphic megakaryocytes with multilobulated nuclei and increase of moderate erythro-megakaryocytic (EM) hyperplasia to marked trilinear erythro-megakaryo-granulocytic hypercellular bone marrow with dilated sinuses are the specific diagnostic features of early and classical untreated PV (Figures 6 and 7). ET may precede PV for many years to more than a decade. Prefibrotic EMGM/PMGM (Tables 5 and 6) is a distinct MPD without features of PV in blood and bone marrow (Figure 8). The

<table>
<thead>
<tr>
<th>Prognosis Group</th>
<th>Criteria</th>
<th>Score</th>
<th>Clinical Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very favorable</td>
<td>Hemoglobin normal &gt;12 g/dl, no anemia. No fibrosis of the bone marrow, EMGM</td>
<td>Score 0</td>
<td>Very early</td>
</tr>
<tr>
<td>Favorable</td>
<td>Hemoglobin &gt;10 g/dl, slight anemia</td>
<td>Score 1</td>
<td>Early</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Hemoglobin &gt;10 g/dl, slight anemia, but no other adverse sign*</td>
<td>Score 2</td>
<td>Over</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>Two adverse signs*</td>
<td>Score 3</td>
<td>Advanced</td>
</tr>
<tr>
<td>Very Unfavourable</td>
<td>More than 2 adverse signs*</td>
<td>Score 4</td>
<td>Endstage</td>
</tr>
<tr>
<td>Adverse signs*</td>
<td>Hemoglobin &lt;10 g/dl, blast PB &gt;1%, precursors WBC. in PB &gt;10%, serum LDH &gt;3 times upper limit, leukopenia &lt;3, leucocytose &gt;20 or &gt;30, thrombocytopenia &lt;100 x 10^9/l constitutional symptoms, massive splenomegaly, cytogenetic abnormality.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rotterdam scoring system of EMGM/IMF**

1. A hemoglobin <12 mmol/l and no adverse signs predicts a favorable prognosis, score 0.
2. A hemoglobin <10 mmol/l and not adverse signs predict a favorable prognosis, score 1.
3. A hemoglobin <10 mmol/l, but absence of any other adverse sign was associated with significantly shortened survival in all studies, intermediate prognosis, score 2.
4. The presence of two of the above mentioned adverse signs predicts a poor prognosis, score 3.
5. The presence of more than two of the above mentioned adverse signs predicts a very poor prognosis, score 4.

**Table 6:** Clinical and laboratory characteristics for prognosis prediction in essential or primary megakaryocytic granulocytic myeloproliferation EMGM/PMGM (IMF) patients according to the 1999 rotterdam scoring system.
histopathology of EMGM/PMGM is dominated by atypical large and immature megakaryocytes with cloud-like immature nuclei, which are not seen in prefibrotic ET and PV at diagnosis and during follow-up. Myelofibrosis is not a feature of ET at diagnosis and during long-term follow-up. Myelofibrosis, which is secondary to myeloid metaplasia of bone marrow proliferation (myeloproliferation), and myeloid metaplasia of the spleen (splenomegaly) constitute a prominent feature and usually progress more or less rapidly during the natural history of PV and PMGM. Life expectancy is normal in normocellular ET. Normal in the early stages of prodromal and classical stages of PV, but significantly shortened in the thrombocythemic hypercellular EMG stage of PV in the various fibrotic stages of PMGM. These clinical and pathological characteristics of the MPDs, by including bone marrow histopathology, enables clinicians and pathologists to clear-cut distinct between normocellular ET, prodromal PV, classical PV hypercellular PV vs. the prefibrotic and fibrotic stages of EMGM/PMGM.

The ECP manuscript on diagnosis and treatment of PV and possible future study designs of the International PVSG by Michiels, Barbui, Finazzi, Fruchtman, Kutti, Rain, Silver, Tefferi and Thiele in 2000 describes clinicopathological criteria to distinct the six sequential stages proposed by Wasserman and Michiels (Figure 2 and Tables 6 and 7) in the natural history of newly diagnosed PV patients. The European Working Group on MPD (EWG.MPD founded and chaired by Michiels 1998-2006) extended and modified the PVSG diagnostic criteria of ET, PV and PMF into normocellular ET at platelet count above $400 \times 10^9/L$, five stages of PV and PMGM as the third MPD entity by including bone marrow histology 1975-2005. From the results of the USA and French PVSG prospective randomized clinical trials in PV showing leukemogenicity of P32 and chlorambucil as compared to phlebotomy, it became evident at the first International MPD Workshop in Rotterdam (1998) that new prospective randomized clinical trials (RCT) are warranted in previously untreated early classical and hypercellular stages of PV. Such RCTs should focus on comparing interferon-alfa, a non leukemogenic myeloreductive biological modifier versus a potential leukemogenic myelosuppressive treatment modality. Hydroxyurea appeared to be the least leukemogenic myelosuppressive agent as compared to P32 and Busulfan in long-term prospective clinical PV-studies extending treatment observation periods of more than 10

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**Figure 9:** Survey of 363 myeloproliferative neoplasm (123 essential thrombocytemia, ET, 190 polycythemia vera, PV and 50 myelofibrosis, MF) patients: 93% of PV, 71% of ET and 37% of MF were on aspirin; 6% of ET, 78% of PV and 9% of MF were treated with phlebotomy. Because of symptomatic MNP disease burden 31% of ET, 29% of PV and 30% of MF were on treatment with hydroxyurea and 16% of ET, 16% of PV and 4% of MF were on treatment with pegylated interferon (PegasysR).
years. The rational for using pegylated interferon (Intron or Pegasys) as a first-line treatment option in newly diagnosed PV patients include its effectiveness to abate constitutional symptoms and to induce complete hematological remission thereby avoiding phlebotomy, iron deficiency, and microcytosis associated with hydroxyurea. Moreover, pegylated IFN-alpha may prevent or delay the development of myelofibrosis if used early and classical stage of previously untreated PV [60]. Clinicians will be reluctant to postpone or delete the use of hydroxyurea early in the course of PV as long as low dose aspirin on top of phlebotomy aiming at a hematocrit of 0.40 is used to keep the PV patient as healthy as possible [51,60]. Low dose aspirin will prevent the microvascular thrombotic complications in ET and in thrombocythemia associated with PV in remission after phlebotomy but lacks myeloreductive and suppressive activity [58,67-69]. Selective control of megakaryocyte maturation will predict a significant reduction of microvascular complications in ET and early stages of prodromal and classical PV and reduction of a hematocrit of 0.40 is used to keep the PV patient as healthy as possible [51,60]. Low dose aspirin will prevent the microvascular thrombotic complications in ET and in thrombocythemia associated with PV in remission after phlebotomy but lacks myeloreductive and suppressive activity [58,67-69]. Selective control of megakaryocyte maturation will predict a significant reduction of microvascular complications in ET and early stages of prodromal and classical PV and reduction of a hematocrit of 0.40 is used to keep the PV patient as healthy as possible [51,60]. Low dose aspirin will prevent the microvascular thrombotic complications in ET and in thrombocythemia associated with PV in remission after phlebotomy but lacks myeloreductive and suppressive activity [58,67-69]. Selective control of megakaryocyte maturation will predict a significant reduction of microvascular complications in ET and early stages of prodromal and classical PV and reduction of a hematocrit of 0.40 is used to keep the PV patient as healthy as possible [51,60]. Low dose aspirin will prevent the microvascular thrombotic complications in ET and in thrombocythemia associated with PV in remission after phlebotomy but lacks myeloreductive and suppressive activity [58,67-69].

Table 7: Six stages of ET→PV according to Wasserman and Michiels.

<table>
<thead>
<tr>
<th>Stage</th>
<th>0ET</th>
<th>1PV</th>
<th>2PV</th>
<th>3PV PV MF</th>
<th>4</th>
<th>5 Spent Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemoglobin (mmol/l)</td>
<td>N/↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N/↑</td>
</tr>
<tr>
<td>Erythrocytes &gt;6 × 10⁹/l</td>
<td>N/↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N/↑</td>
</tr>
<tr>
<td>Male&gt;36ml/kg</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N/↑</td>
</tr>
<tr>
<td>Female&gt;32 ml/kg</td>
<td>N</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N/↑</td>
</tr>
<tr>
<td>Hematocrit</td>
<td>N/↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>N/↑</td>
</tr>
<tr>
<td>Platelets × 10⁹/l</td>
<td>&lt;400/&gt;400</td>
<td>&lt;400</td>
<td>&gt;400</td>
<td>&gt;1000</td>
<td>Variable</td>
<td>N/↑</td>
</tr>
<tr>
<td>Leukocytes × 10⁹/l</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Leukemoid reaction</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Spleen length diameter (cm) or scan or echogram</td>
<td>&lt;12</td>
<td>12-15</td>
<td>&lt;12</td>
<td>&lt;15</td>
<td>&gt;15</td>
<td>Large</td>
</tr>
</tbody>
</table>

**Bowel Marrow Biopsy**

| Cellularity | N/↑ | N/↑ | ↑ | ↑ | ↑ | ↑ |
| Megakaryocytes | ↑ | ↑ | ↑ | ↑ | ↑ | ↑ |
| Myelofibrosis | 0 | 0 | 0/1 | 1/2 | 2/3 | 3 |
| Spontaneous EEC | + | + | + | + | + | + |
| PVR 1-gene | + | + | + | + | + | + |

N=Normal, =Absent, ++=Present, ↑=increased, ↑↑=Pronounced increased.

Six clinicopathological stages of PV according to Wasserman and Michiels: 0: latent or subclinical prefibrotic PV; 1: the so called erythremia of Wasserman the so called idiopathic erythrocytosis of Pearson; 2: early stage PV with no significant or slight splenomegaly and no or early MF; 3: overt plethoric stage of PV with various degrees of pronounced splenomegaly and MF; 4: advanced myelofibrotic or spent phase PV; 5: transformation to MSDS and/or AML.

References

polycythemia vera and prefibrotic and fibrotic agnogenic myeloid metaplasia.


