Anagrelide for Thrombocytosis in Myeloproliferative Disorders

A Prospective Study to Assess Efficacy and Adverse Event Profile

Michael Steurer, M.D.[1]
Guenther Gastl, M.D.[1]
Wieslaw-Wiktor Jedrzejczak, M.D.[2]
Robert Pytlik, M.D.[3]
Werner Lin, M.D.[4]
Ernst Schlögl, M.D.[5]
Heinz Gisslinger, M.D.[6]

[1] Division of Hematology and Oncology, Medical University of Innsbruck, Innsbruck, Austria.

[2] Department of Hematology and Oncology, Medical University of Warsaw, Warsaw, Poland.

[3] University Hospital Kálovské Vinohrady, Oddelení Klinicke Hematologie Srobarova, Prague, Czech Republic.

[4] Department of Internal Medicine and Dialysis Unit, Landeskrankenhaus Villach, Villach, Austria.

[5] Department of Internal Medicine III, Hematology and Oncology Centre, Hanusck Hospital, Vienna, Austria.

[6] Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Vienna, Austria.

Address for reprints: Heinz Gisslinger, M.D., Department of Internal Medicine I, Division of Hematology and Blood Coagulation, Medical University of Vienna, Währinger-Gürtel 18-20, A-1090 Vienna, Austria; Fax: (011) 00431-402-69-30, E-mail: heinz.gisslinger@meduniwien.ac.at

BACKGROUND. Although the platelet count does not correlate with the rate of thrombosis, there is evidence that a strict control of the platelet count decreases the incidence of thromboembolic complications in essential thrombocythemia. In the current study, the authors evaluated the efficacy and tolerability of anagrelide in thrombocytosis associated with myeloproliferative disorders.

METHODS. The study cohort comprised 97 patients ($n = 69$ females, $n = 28$ males) with a median age of 59 years (range, 21–80 years). Patients with essential thrombocythemia ($n = 79$) or with thrombocytosis due to polycythemia vera ($n = 16$) or to chronic idiopathic myelofibrosis ($n = 2$) were enrolled in the multicenter, prospective study. Patients received anagrelide at a starting dose of 0.5 mg twice per day, which was then adjusted for each patient.

RESULTS. Treatment with anagrelide resulted in a rapid decrease in the platelet count, from a median baseline platelet count of 743×10^9/L to a median platelet count of 441×10^9/L after 6 months ($P < 0.0001$). The proportion of patients with a platelet count $< 600 \times 10^9$/L increased from 30% at baseline to 77% after the 6-month study period. The rate of major thrombotic complications significantly decreased from 5% to 2% ($P = 0.2568$). For patients with essential thrombocythemia, the reduction of major thromboembolic complications was significant ($P = 0.0455$). The rate of minor thromboembolic complications decreased from 25% before anagrelide treatment to 14% during anagrelide treatment ($P = 0.0278$). No severe side effects were observed during the study period. There was, however, evidence that concomitant administration of acetylsalicylic acid may increase bleeding tendency.

CONCLUSIONS. Anagrelide was an effective and well tolerated treatment modality for reducing platelet counts in both newly diagnosed and pretreated patients with thrombocytosis due to myeloproliferative disorders. *Cancer* 2004;101:2239–46.
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KEYWORDS: anagrelide, essential thrombocythemia, polycythemia vera, idiopathic myelofibrosis, thromboembolic complications.

High platelet counts in essential thrombocythemia (ET), polycythemia vera (PV), and in the early stage of chronic idiopathic myelofibrosis (CIMF) are associated with a number of life-threatening complications (e.g., deep venous thrombosis with pulmonary embolism, stroke, myocardial infarction, or life-threatening hemorrhages). Also, symptoms due to microcirculatory disturbances such as peripheral paresthesia of the extremities, headache, dizziness, and visual disturbances are very common. Up to 76% of patients with ET experience arterial thrombosis, $\leq 15\%$ have venous thrombosis, $\leq 63\%$ have hemorrhage, and $\leq 69\%$ encounter functional symptoms. The esti-

mated risk for thrombotic episodes is 6.6% per patient-year, and in patients > 60 years, this incidence increases to 15.1%.[1–4]

The risk of complications has been correlated with predisposing factors such as previous clinical events, long duration of the disease, and age.[1,3,4] Although the platelet count does not correlate with the rate of thrombosis, there is evidence that a strict control of the platelet count decreases the incidence of thromboembolic complications in ET.[5] High-risk patients have been defined to be patients with platelet counts > 1500 × 10^9/L, patients with a history of major thrombosis, patients with the presence of vascular disease, patients with a history of spontaneous or major bleedings, and patients with age > 60 years.[2] It is, therefore, generally accepted that high-risk patients with ET should receive platelet-lowering treatment to reduce the risk of thromboembolic complications.[3] There is also increasing evidence that younger patients and patients with platelet counts < 900 × 10^9/L could benefit from platelet-lowering treatment. However, the use of platelet-lowering agents in these patients is still controversial.[1–3,6]

Hydroxyurea is generally considered to be the treatment of choice for thrombocytosis associated with chronic myeloproliferative disorders although interferon-alpha (IFN-α) may be preferred for treatment of younger patients (< 60 years).[2,7] However, both drugs also have disadvantages. For example, hydroxyurea may be associated with potential leukemogenicity if administered > 7–10 years. IFN-α has to be administered subcutaneously and is poorly tolerated, mainly in the elderly. Furthermore, neither of these two drugs lowers platelet numbers selectively.[8–10] Anagrelide (Imidazo(2,1-b)quinazolin-2(3H)-one,6,7-dichloro-1,5-dihydromonohydro-chloride) is a new treatment option for patients with thrombocytosis associated with chronic myeloproliferative disorders.[11,12] It has a selective mechanism of action on platelets, is administered orally, and has no evidence of long-term leukemogenicity. Experience with the use of anagrelide for thrombocythemic patients has been documented in a large cohort of patients and anagrelide has been registered in the United States since 1997.[13] The long-term use of anagrelide for ≤ 10 years recently has been described.[14] Approximately 1000 patients with thrombocytosis due to chronic myeloproliferative disorders have been documented as having been treated with anagrelide.[11–20] However, most of these reports are retrospective analyses of patients receiving anagrelide therapy and do not allow an evaluation of the benefit/risk ratio of such a treatment modality. In the current paper, we report the results of a prospective Phase II trial that was designed to investigate the efficacy and tolerability of anagrelide in the clinical routine management of patients with increased platelet counts associated with ET, PV, or CIMF.

MATERIALS AND METHODS
Patients
Ninety-seven patients with newly diagnosed or pretreated ET, PV, or CIMF were recruited at 12 centers between April 2000 and April 2002. To be included in the study, newly diagnosed patients had to qualify as high-risk patients. Pretreated patients had to be refractory in terms of inadequate reduction of platelet counts or intolerance to hydroxyurea or IFN-α, or had to fulfill ≥ 1 of the following inclusion criteria: a platelet count > 1500 × 10^9/L, clinical symptoms associated with thrombocythemia and a platelet count between 600 × 10^9/L and 1500 × 10^9/L, asymptomatic patients with a platelet count < 1500 × 10^9/L and an increase in platelet count by > 300 × 10^9/L within the last 3 months, or asymptomatic patients with a platelet count > 600 × 10^9/L and a history of thrombotic/hemorrhagic complications.

Patients were excluded if they had Grade 4 cardiac disease, or if they had severe renal (creatinine clearance < 30 mL/min) or hepatic function impairment (aspartate aminotransferase and alanine aminotransferase levels > 5 times normal levels). Pregnant women or females who were not practicing contraception were also excluded. Patients were withdrawn from the study if they had anaphylactoid reactions, intolerable side effects, or Grade 3/4 adverse events.

The study was designed and conducted in accordance with the ethical principles of Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by local ethics committees, and written informed consent was obtained from all patients before any study procedures were initiated.

Study Design and Treatment
The study was planned as a Phase II international multicenter study. For each patient, safety and efficacy analyses were performed over a 6-month period. Screening assessments were performed ≥ 1 month before the commencement of the study.

Anagrelide was administered to patients on Day 0 at a recommended starting dose of 0.5 mg twice per day. After 2 weeks, the dose was increased to 1 mg twice per day, and then adjusted for each patient. Doses were not changed by > 0.5 mg/day within any given week, and if feasible, patients were maintained at their prescribed anagrelide dose for the duration of the trial. In patients pretreated with hydroxyurea or

IFN-α, it was allowed to combine anagrelide with one of those compounds.

For patients with hepatic, renal, or cardiac disease, anagrelide was only administered under close supervision. A number of physical examinations were performed, including measurement of blood pressure, heart rate, and body temperature. Laboratory tests were also performed and included complete blood cell counts with differential count, renal and hepatic function tests, monitoring of electrolyte levels, and measurement of partial thromboplastin time and fibrinogen levels. There were no restrictions regarding the timing of food intake during the trial. Also, there were no restrictions regarding previous cytoreductive drug therapy or other drugs. Patient diary cards were used to record drug administration, and drug containers were checked during follow-up.

Efficacy Assessment

The primary efficacy variable was defined as the number of platelets. Platelet counts were analyzed at the following time points: at diagnosis, before the start and at the end of the previous cytoreductive treatment, at screening, at the start of anagrelide treatment, during treatment on Days 7, 14, 21, and 28, and at Months 2, 3, 4, 5, and 6. Platelet count was used as a surrogate marker for clinical complications, as there is a correlation between lowering the platelet number and risk of complications such as thrombosis, hemorrhage, and stroke.[2,5] Contingency tables were used to analyze within-group changes in platelet counts, specifically the preshift–postshift in platelet counts with regard to clinical benchmark values of the following platelet levels: $< 600 \times 10^9$/L, 600–900 $\times 10^9$/L , and $> 900 \times 10^9$/L.

Secondary (supportive) efficacy parameters were defined as the rate of clinical complications before and during anagrelide therapy, and as the number of patients achieving response. For assessment of thromboembolic complications occurring in the 6 months before study entry, a specific patient history and a medical report of the corresponding event were required. According to the severity of the thromboembolic complication, they were differentiated as major or minor. Major complications were defined as stroke, myocardial infarction, peripheral arterial disease, ileofemoral venous thrombosis, pulmonary infarction, thrombosis of the portal vein, Budd–Chiari syndrome, or bleeding (decrease in hemoglobin [Hb] level ≥ 1 g/dL or red blood cell [RBC] transfusions required). Minor complications were defined as transitory ischemic attacks, angina pectoris, erythromelalgia or other microcirculatory disturbances, superficial thrombophlebitis, or bleeding (Hb level decrease < 1 g/dL and no RBC transfusions required).

Response was defined as complete, partial, or failure to respond. A complete response was the normalization of platelet counts ($< 450 \times 10^9$/L) or a very good partial response ($< 600 \times 10^9$/L) for a period of 4 weeks. A partial response was a decrease in platelet counts by $> 50\%$ of the initial value for a period of 4 weeks, without reaching levels defined as a complete response. Failure to respond was no decrease or a decrease of $\leq 50\%$ in the platelet count. In addition, patients were analyzed according to the following subgroups: ET versus PV, no previous cytoreductive therapy versus previous cytoreductive therapy, and no history of complications versus a history of complications.

Safety Assessment

The following safety variables were measured: number of patients discontinuing therapy because of adverse events, lack of compliance, or other specific reasons; vital signs; leukocyte and RBC counts with differential count; blood chemistry; electrolyte levels; prothrombin time; and occurrence of clinical adverse events. Adverse events were recorded using Medical Dictionary for Regulatory Activities (MedDra) terminology. Adverse events occurring more than once were considered as one event, and were reported as severe.

Statistical Analysis

All patients included in the study who received at least one dose of medication were entered into the intention-to-treat analysis. For the current study, the per-protocol population was identical to the intention-to-treat population. All patients included in the study who received at least one dose of medication and had at least one postbaseline safety evaluation were also included in the safety analysis. Demographic and background information was summarized and displayed using descriptive statistical techniques. For categorical variables, frequency tables were presented. For continuous variables, descriptive statistics such as mean, median, standard deviation, and range were tabulated. Nonparametric procedures were used for all statistical analyses. In addition to P values, all results were calculated by using Mann–Whitney estimators as nonparametric effect sizes, together with their 2-sided 95% confidence intervals (CI). Effect sizes and 95% CIs for the within-group comparison for major and minor complications were calculated by using the generalized McNemar test for kxk-ordered categories. For the response rates (complete and partial responders), 2-sided 95% CIs were used.

Platelets (10^9/L): absolute values on Day 0 (baseline) vs. Month 6
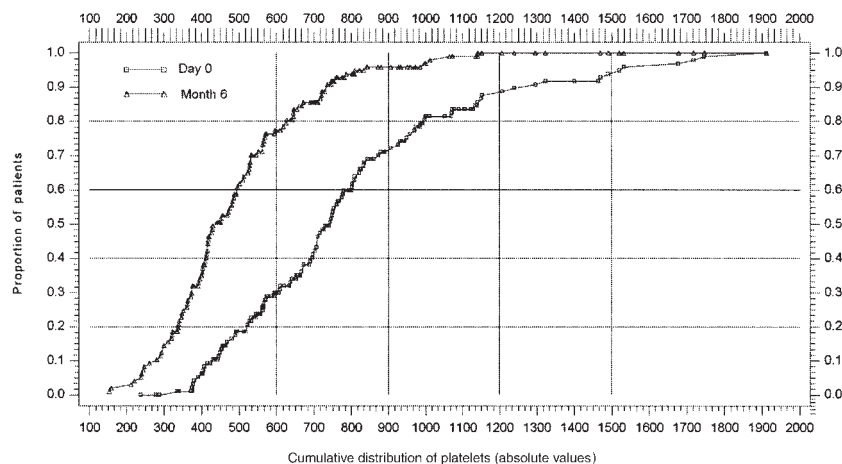
FIGURE 1. Cumulative distribution of platelets ($\times$ 10^9/L) at the start and end of the trial period (intention-to-treat population)

RESULTS

Patients and Anagrelide Dose

Ninety-seven patients participated in the study ($n = 79$ patients with ET, $n = 16$ with PV, and $n = 2$ patients with CIMF). The median age of the patients was 59 years (range, 21–80 years), and 69 patients were female. Fifty-five patients had a history of thromboembolic events and the majority of patients ($n = 69$) had received previous therapy. Previous therapies included hydroxyurea for most patients ($n = 51$), followed by IFN-α ($n = 34$) and busulphan ($n = 5$) or melphalan ($n = 1$). Of the 97 patients entering the study, 88 patients completed the study period of 6 months according to the protocol. The daily dose of anagrelide increased during the study from a median of 1.0 mg (range, 0.5–2.0 mg) to a median of 2.0 mg (range, 0.5–4.5 mg). In approximately 90% of patients, the maximum dose of anagrelide, 0.5–3.0 mg, was sufficient to achieve the observed results. At baseline, 19 patients received concomitant therapy with IFN-α ($n = 9$) or hydroxyurea ($n = 10$). This number decreased to 7 patients (4 and 3 patients, respectively) after 6 months of treatment. The other 12 patients were switched to single-agent anagrelide during the study period.

Primary Efficacy Measures

Platelet counts decreased significantly during the 6-month study period from a median baseline count of 743×10^9/L (range, $335–1.912 \times 10^9$/L) to a median count of 441×10^9/L (range, 153×10^9/L to 1.141×10^9/L; $P < 0.001$ using the generalized McNemar test). Fifty patients qualified as complete responders and 25 patients had a very good partial response. The overall (complete, very good partial, and partial, $n = 77$) response rate was 79% when an intention-to-

treat analysis was applied. Of the patient subgroups, the highest overall response rate of 82% was achieved in patients with no previous cytoreductive therapy. The lowest rate of 75% occurred among patients with PV. Cumulative distribution analyses of platelet counts showed a marked decrease after 6 months, irrespective of baseline platelet value (Fig. 1). The before and after comparisons of platelet counts were not only highly statistically significant but also relevant in respect to effect size. The extent of the efficacy responses indicated a medium-sized superiority already after 7 days (Mann–Whitney estimate > 0.64) and a large superiority for the final results after 6 months (Mann–Whitney estimate = 0.76). The response results continuously improved during the 6-month study period (Fig. 2). The cumulative distribution analysis for patients with previous cytoreductive therapy was almost identical to that of previously untreated patients, indicating a similar effect on lowering the platelet counts in patients with previous cytoreductive therapies (Fig. 3). When three benchmark categories of platelet counts were taken, marked changes within the categories were observed (Table 1). Fifty-four patients shifted to a lower benchmark category, whereas three patients were shifted to a higher category. The proportion of patients with a platelet count < 600×10^9/L and < 900×10^9/L increased from 30% and 71%, respectively, at baseline to 77% and 96%, respectively, after the 6-month study period.

Secondary Efficacy Measures

During the 6 months before the study, the rate of major thromboembolic complications was 5%. At the end of the study, this rate had decreased to 2% (Mann–
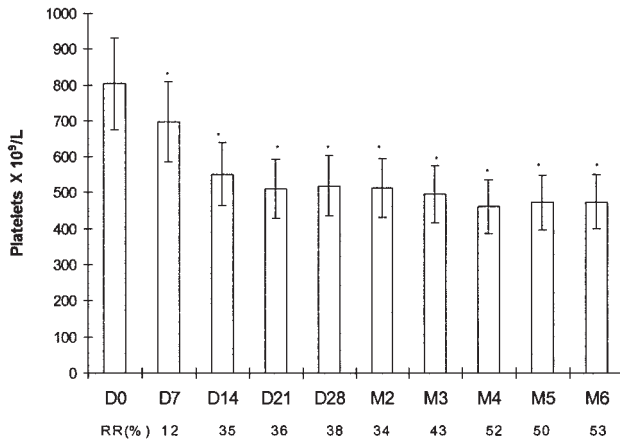
FIGURE 2. Changes in platelet counts after the start of treatment with anagrelide over 6 months (mean $\pm$ standard deviation). *$P < 0.001$ attained with the generalized McNemar test. RR: response rate. RR $=$ percentage of patients with platelet counts $< 450 \times 10^9$/L). D: day; M: month.

Whitney estimate $= 0.52$, 95% CI $= 0.46–0.54$, $P = 0.2568$, marginal superiority; Fig. 4). For the subgroup ET, superiority of anagrelide treatment compared with the pretreatment period was proven by the lower boundary of the 95% CI that was > 0.50 (95% CI $= 0.50–0.55$, $P = 0.0455$). The 6 patients with major thromboembolic or bleeding complications (ischemic or hemorrhagic stroke, myocardial infarction, peripheral arterial disease, pulmonary embolism) within the 6 months before initiation of anagrelide remained without complications during the study period. Two patients had major thrombotic complications during treatment with anagrelide. In 1 patient, who developed coronary artery disease after 1 month, the pretreatment platelet count (748×10^9/L) could not be reduced by anagrelide after 6 months of treatment (809×10^9/L). The other patient developed myocardial infarction after 6 months despite a normalization of the platelet counts.

Minor Thromboembolic Complications

At the start of the study, the rate of minor thromboembolic complications was 25%. After the study period, this rate had decreased to 14% (Mann–Whitney estimate $= 0.56$; Fig. 4). For both the intention-to-treat population and the subgroup with ET, superiority of anagrelide treatment compared with the pretreatment period was proven because the lower boundary of the 95% CI was > 0.50 ($P < 0.05$). Twenty-three patients had minor thromboembolic complications within 6 months before initiation of anagrelide. For 15 patients, these symptoms disappeared during anagrelide treatment. The remaining 8 patients had either cerebral microcirculatory disturbances ($n = 3$), peripheral microcirculatory disturbances ($n = 2$), erythromelalgia ($n = 1$), or thrombophlebitis ($n = 1$). Seven patients had minor thromboembolic symptoms despite initiation of anagrelide treatment. Three of them had a history of major thromboembolic symptoms before anagrelide treatment. Three of the patients developed these symptoms despite normal platelet counts after anagrelide therapy.

Safety

Eighty-eight patients were treated with anagrelide for 6 months. Nine patients discontinued the study prematurely, and three died. Two patients withdrew informed consent—one because of a wish for pregnancy and one because of an adverse event. In addition, one patient was withdrawn due to major protocol violation, one due to a lack of compliance, and two due to adverse events (dyspepsia and palpitations, and increased liver transaminase levels, respectively). Two patients received the therapy for 3 weeks, 2 for 2 months, 3 for 3 months, and 1 patient for 5 months.

In general, anagrelide was well tolerated, and 329 adverse events were recorded for 69 patients. During the study, 28 serious adverse events were observed in 21 patients, including 3 deaths. The causes of death were dissecting aortic aneurysm, pulmonary embolism that occurred during hospitalization for bowel obstruction, and in one case cardiac arrest was suspected. None of these deaths was considered to be related to the study drug. Only four serious adverse events were rated as possibly being related to the study drug, i.e., congestive heart failure, bleeding after bone marrow biopsy, cerebral ischemia, and transitory ischemic attack. Ninety-four percent of nonserious adverse events were rated as mild or moderate according to the National Cancer Institute Common Toxicity Criteria, including headache, diarrhea, and palpitations (Table 2). Their frequency decreased markedly during the study period. Only 8% of all adverse events were classified as a "probable/likely" in relation to the study drug. Eleven patients had at least one bleeding event through the study period. The majority of bleeding events occurred in patients who received low-dose acetylsalicylic acid as concomitant medication (nine patients vs. two patients; Table 3). The sites of bleeding were with decreasing frequency: epistaxis, subcutaneous hematoma, gingival bleeding, intramuscular hematoma, upper gastrointestinal tracts, bleeding after bone marrow biopsy, and hemorrhagic stroke.
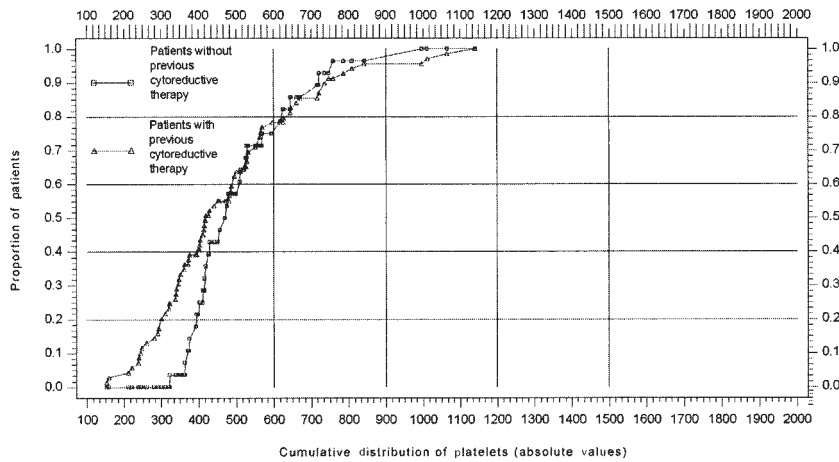
Platelets (10⁹/L): absolute values at Month 6

FIGURE 3. Cumulative distribution of platelet counts ($\times$ 10^9/L) at the end of the trial period (patients without cytoreductive therapy vs. patients with cytoreductive therapy).

TABLE 1
Benchmark Categories of Thrombocytes on Day 0 Versus Month 6

	Thrombocytes ($\times 10^9$/L) (%)		
	≤ 600	> 600 to $\leq$ 900	> 900
Day 0	29 (30)	40 (41)	28 (29)
Month 6	75 (77)	18 (19)	4 (4)

TABLE 2
Development of the Most Frequent Adverse Events
(Percentage of Patients)

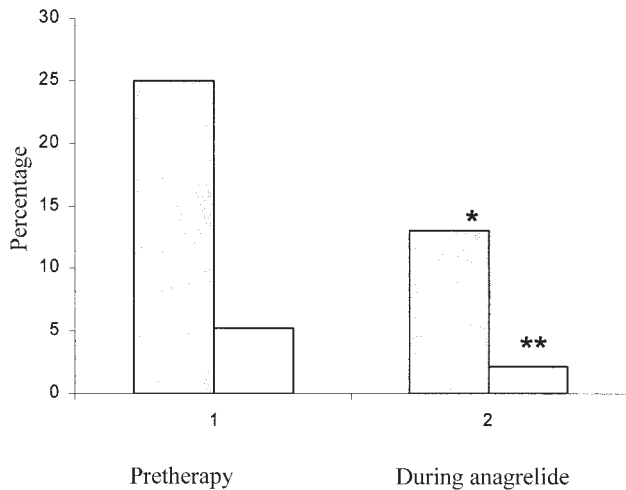| Treatment period	Month 1	Months 2–3	Months 4–6
Headache	25	11	10
Diarrhea	8	8	2
Palpitation	8	2	2
Common cold	1	5	5
Weakness	3	3	1
Fatigue	4	1	2
Vertigo	4	3	0
Cough	2	1	2
Dizziness	4	2	0

FIGURE 4. Myeloproliferative disorder-associated thromboembolic complications (6 months pretherapy vs. 6 months posttherapy), minor complications, major complications. * Mann–Whitney estimate of 0.56, P = 0.0278. **Mann–Whitney estimate of 0.52, P > 0.05. The P value for patients with essential thrombocythemia was 0.0465. Shaded bars: minor complications; open bars: major complications.

DISCUSSION

The current investigation shows that anagrelide is an effective platelet-lowering agent, not only for newly diagnosed patients with a high initial platelet count, but also for patients pretreated with chemotherapy or IFN-α. Our data provide evidence that anagrelide achieves a marked and fast response of platelet counts in ET, PV, or CIMF, which translates into a reduction of clinical complications. After 6 months of anagrelide treatment, the proportion of patients with a reduction of platelet count $< 600 \times 10^9$/L was markedly increased and, accordingly, the rate of major and minor thromboembolic complications was also significantly reduced.

The reduction of thromboembolic events with a decrease in platelet counts achieved in our investigation is in accordance with the results of a prospective randomized trial on prevention of thrombosis in high-risk patients with ET treated with hydroxyurea.[2] Although our data on clinical symptoms were evaluated retrospectively during the observation period of 6

TABLE 3
Patients with Bleeding Events with and without ASA as Concomitant Medication at Each Visit

Characteristics	Baseline	Day 7	Day 14	Day 21	Day 28	Month 2	Month 3	Month 4	Month 5	Month 6
No. of patients (total)	97	95	96	91	94	93	90	88	87	89
No. of patients receiving ASA	53	49	51	51	48	50	44	47	43	47
No. of patients with ASA and bleeding	0	0	0	1	1	4	2	3	1	1
No. of patients without ASA and bleeding	0	0	0	0	0	0	1	0	1	0

ASA: acetylsalicylic acid.

months before initiation of anagrelide, our results confirm data published earlier, that strict control of platelet counts may improve the rate of clinical symptoms in thrombocythemic patients.[5,7]

Current treatment recommendations for thrombocytosis associated with chronic myeloproliferative disorders aim at a reduction in the platelet count according to the patients' risk status. Platelet counts between 1000×10^9/L and 1500×10^9/L or between 600×10^9/L and 1000×10^9/L associated with additional risk factors like age > 60 years or a history of thromboembolic complications are regarded as indications for cytoreductive therapies. However, it has also been shown that a high proportion of patients with low-risk parameters, e.g., platelet counts $< 600 \times 10^9$/L or young patients, can exhibit a high rate of clinical complications which deserves a reduction of platelet counts to normal values.[6,21,22] Because life expectancy is not markedly shortened in patients with ET as well as in most of the younger patients with thrombocythemic PV and in particular in patients with early-stage CIMF with thrombocytosis, long-term treatment through decades may be necessary to prevent thromboembolic complications.[2,4,21–23] Although hydroxyurea is considered to be a standard platelet-lowering agent in this patient group, there is still concern regarding a potential leukemogenic effect associated with its long-term use.[8] As alternative treatment agents, which are unlikely to be leukemogenic for thrombocythemic patients with myeloproliferative disorders, have become available, mainly younger patients should be switched to nonchemotherapeutic agents like anagrelide or IFN-α. Our results have shown that anagrelide is well tolerated. The most common adverse events observed were headache, diarrhea, and palpitations. Headache and palpitations may be caused by the vasodilating and positive inotropic effects of the drug, which ceased after a few weeks of treatment. One of the most important findings of this investigation is, however, that a high percentage of patients who receive a combination of anagrelide and low-dose acetylsalicylic acid were prone to bleeding. Despite controlled platelet counts,

we observed minor bleeding events in 13% of patients who received anagrelide in combination with low-dose acetylsalicylic acid compared with 2% of patients who received anagrelide alone. This markedly exceeds previously reported rates of hemorrhagic events among patients with ET or PV and anagrelide treatment in combination with acetylsalicylic acid.[14,24] Most bleeding events occurred after a treatment period of > 1 month. Anagrelide, an inhibitor of cyclic adenosine monophosphate phosphodiesterase, was originally developed as an inhibitor of platelet aggregation. The concentrations needed to exert antiaggregation effects are reported to be ≥ 10 times higher than those needed for controlling thrombocythemia.[25] Thus, it is generally acknowledged that at doses used to treat myeloproliferative disorders, no antiaggregating effect is detectable.[12,26,27] Furthermore, low-dose acetylsalicylic acid alone also seems to be safe and effective in preventing thrombosis in patients with ET.[28] However, in the absence of appropriate in vivo or in vitro studies, a possible inhibitory impact of long-term therapy with anagrelide in combination with acetylsalicylic acid on platelet function in patients with myeloproliferative diseases cannot be excluded. Therefore, the combination of these two drugs has to be used with extreme caution and acetylsalicylic acid should not be administered in combination with anagrelide in patients who have a history of bleeding. Conversely, when anagrelide was combined with IFN-α in younger patients or with hydroxyurea in elderly patients, the dosage and consecutive side effects of both drugs could be reduced and the combination did achieve a pronounced platelet-lowering effect. From the data provided by our prospective study, we concluded that anagrelide is an effective and well tolerated platelet-lowering agent in patients with myeloproliferative disorders and thrombocytosis. Despite using a moderate dosing regimen of anagrelide, it was possible to normalize platelet counts in approximately half of the patients. The combination of anagrelide with hydroxyurea or with IFN-α is feasible and might lead to better tolerability and efficacy, rendering more patients eligible for anagrelide treatment. The results

of ongoing randomized studies comparing hydroxyurea with anagrelide will further assess their benefit/risk ratio in thrombocythemic patients with chronic myeloproliferative disorders.

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