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A long-term study of young patients with essential thrombocythemia treated with anagrelide

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A B S T R A C T

Background and Objectives. Essential thrombocythemia (ET) can be complicated by life-threatening thrombosis and has a risk of converting into acute leukemia. Cytoreductive therapy may reduce the risk of thromboembolic complications. Herein, we report the results of a long-term study of patients with ET treated with anagrelide to control thrombocytosis.

Design and Methods. Thirty-nine (34 evaluable) patients (median age, 33 years; 24 previously untreated) were enrolled between 1989-1996; the mean platelet count prior to therapy was 1197×10^9/L. Only 9 out of 34 evaluable patients were at high risk of thrombosis (platelet count more than 1500×10^9/L). The initial dose of anagrelide (0.5 mg/bid for 7 days) was increased by 0.5 mg/day (maximum dose: 3 mg/day) until a response was seen.

Results. A complete response (platelets < 450×10^9/L for >1 month) was seen in 15 /34 (44%) patients and a partial response (platelets 450-600×10^9/L for >1 month) was seen in 17/34 (50%), so that the some kind of response was seen in 32/34 (94%) of the patients at a median time of 4.2 months after starting treatment. Seventeen patients (50%) are still being treated and have achieved platelet control for a maximum follow-up of 12.5 years. Late onset anemia occurred in 4/39 patients. Three out of 39 patients (8%) had cardiac disorders.

Interpretation and Conclusions. Anagrelide appears suitable for controlling thrombocytosis in ET patients over the long-term. This drug may be used in patients younger than 60 years, with the exclusion of women of child-bearing potential and subjects aged 40-60 years with a history of major thrombotic events. Anagrelide should not be administered to patients with cardiac disorders, and a careful approach to patients should include monitoring of heart function before and during treatment.

Key words: essential thrombocythemia, anagrelide, thrombosis, leukemic transformation.

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Essential thrombocythemia (ET) is a myeloproliferative disorder characterized by excessive proliferation of megakaryocytes and a sustained elevation of platelet count with a relatively benign chronic course.[1,2] Patients may be asymptomatic or may exhibit vascular symptoms.[3] The clinical course of ET is characterized by thromboembolic episodes and, less frequently, by hemorrhagic symptoms. The thrombotic risk in ET is 30% in patients with a prior history of thrombosis and 3% among those with no previous history of thrombosis.[4] For this reason, cytoreductive therapy is given to avoid thrombo-hemorrhagic complications. The life expectancy of ET patients is generally long and similar to that of an age-matched normal population.[5] However, more recently other authors reported that both quality of life and life expectancy significantly decrease in younger ET patients.[6] Progression to acute leukemia is a rare event, occurring in about 3-5% of cases with ET,[7,8] and it may be even rarer in untreated patients.[9,10]

The treatment of ET has evolved from the use of radiophosphorus, or alkylating agents[11,12] to hydroxyurea (HU) as therapy to control thrombocytosis.[13-16] More recently, agents such as recombinant interferon-α (rIFN-α) and anagrelide have been introduced and have been successful in bringing platelet levels down to normal.[17-24] In Europe, four cytoreductive agents are currently used for the treatment of ET: rIFN-α, busulfan, pipobroman, and HU. Busulfan is rarely employed due to its leukemogenic effect. It is unclear whether pipobroman and hydroxyurea increase the risk of conversion into acute leukemia (AL) in ET patients.[25-29] The rIFN-α associated side effects are sometimes so severe that patients tend to withdraw

from treatment.[30] Anagrelide hydrochloride, approved for use in the USA in 1997, is an oral imidazoquinazoline compound that lowers raised platelet counts in patients with ET and related myeloproliferative disorders.[20,31] It selectively acts on bone marrow megakaryocytes by interfering with the maturation process and decreasing platelet production without affecting the erythroid and myeloid progenitor cells.[32,33]

Several studies on therapy with anagrelide have shown that this drug is effective in over 80% of cases.[20-22, 25,34-36] Moreover, successful treatment of a limited number of young patients with ET has also been reported.[37-39] Here, we report the results of a long-term study of young patients with ET treated with anagrelide to control thrombocytosis.

Design and Methods

Enrollment and diagnosis

Thirty-nine young patients with ET began treatment with anagrelide between 1989 and 1996. These patients were enrolled in an open protocol (no. 13.970-301A/301B) for compassionate use of anagrelide in patients with ET by the Bristol-Myers Squibb Company and Roberts Pharmaceutical Corporation. The main criteria for enrollment were: age >18 years, a diagnosis of ET based on the guidelines of the *Polycythemia Vera Study Group*[13,40] (and the revised updated criteria),[3] a platelet count $\geq 900\times10^9$/L in at least two consecutive measurements or between $650\text{-}900\times10^9$/L if symptoms related to ET were present. Pretreated patients could be enrolled if previous therapies had failed or the patients were intolerant of such therapies. Since anagrelide was an experimental drug, in our Institute we excluded patients aged > 60 years for reasons of safety. Patients were excluded if they were pregnant, and those of childbearing age had to be using adequate contraception. A negative pregnancy test was required upon enrollment and periodic pregnancy tests were recommended for those patients who were still liable to become pregnant. At the time of enrollment, any concomitant medication, both prescription and non-prescription drugs, was recorded. Each patient was assessed for suitability prior to being treated and was required to give informed consent before beginning therapy. The study was approved by the Ethics Committee of our Institution.

Treatment

Anagrelide was not a licensed drug in Europe and was first provided by Bristol-Myers Squibb Company, then by Roberts Pharmaceutical Corporation, and now by the Shire Pharmaceutical Group. The drug was available in 0.5 and 1 mg capsules for oral administration. Anagrelide treatment was given on a basis of compassionate use and was discontinued if there were adverse events or lack of efficacy. The therapy schedule was 0.5 mg every 12 hours for 7 days; subsequently, the daily dose was increased by 0.5 mg/day every week until a response was obtained. The dose was not allowed to exceed 3 mg/day. No patient received acetylsalicylic acid during treatment with anagrelide.

Evaluation criteria

The primary end-point was the proportion of patients who responded to treatment. Complete response (CR) was defined as a decrease in platelet count to less than 450×10^9/L lasting for at least 1 month. Partial response (PR) was defined as a platelet count of $450\text{-}600\times10^9$/L lasting for at least 1 month. Those patients who completed at least 1 month of therapy were considered evaluable. Follow-up was defined as the time elapsing from the beginning of therapy to the last measurement or to drug withdrawal. Platelet counts were determined with the H1 and/or H3 Technicon system. The secondary end-points included time to achieve CR or PR, platelet count reduction, the relationship between platelet counts and thrombo-hemorrhagic symptoms and anagrelide dosing.

Full blood counts were recorded every week during the first month of therapy, every 2 weeks during the second month and subsequently every month, and every 3 to 4 months in the steady state responding patients. Side effects were monitored during therapy. Patients were monitored for those drug-related side effects reported by the Anagrelide Study Group,[21] which are generally due to the vasodilatory properties and lactose formulation of anagrelide. All adverse events, regardless of therapy, were recorded in the patient's clinical records. A serious adverse event was defined as any event that was fatal, life-threatening, permanently disabling, or required hospitalization. Other safety assessments included changes from baseline for vital signs and performance status.

Statistical analysis

Statistical studies were performed using the Wilcoxon signed-rank test. Changes in platelet levels from pretreatment, at response, and at the last measurement were calculated and records were kept of daily doses of anagrelide given to elicit a response and for the maintenance dose. Similarly, changes from baseline for hemoglobin concentration, hematocrit, red blood cell, white blood cell, neutrophil, and lymphocyte counts were determined. Calculations were also made regarding dosage at response, during maintenance, and at the occurrence of any adverse events. A p value ≤ 0.05 was considered statistically significant.

Results

Patients' demographic and baseline characteristics

Thirty-nine patients (males 17, females 22) were entered into the study. Their ages at diagnosis ranged from 22-52 years (mean 34, median 33). Fifteen patients (38.5%) had received previous therapy (5 with pipobroman, 3 with rIFN-α, 1 with HU, 2 with HU and rIFN-α, 2 with HU and pipobroman, 1 with rIFN-α and pipobroman, and 1 with HU, rIFN-α, and pipobroman, all given sequentially). Previous therapy had been discontinued because of lack of response in 10 patients and intolerance in 5. There was at least 1 week as a flush-out period before anagrelide was started.

Before beginning therapy with anagrelide, 12/39 (31%) patients had disease-related symptoms: acral paresthesia (4 episodes); headache (3 episodes); cutaneous itching (2 episodes); dizziness (2 episodes); scotoma (2 episodes); Raynaud-like symptoms (1 episode). Eight patients were smokers, and 2 of them had high levels of cholesterol and triglycerides. No patient had been diagnosed, either previously or presently, with cardiovascular diseases, venous/arterial thromboses, or major bleeding events. Prior to starting therapy, their mean platelet count was 1197×10^9/L (range 610-2390×10^9/L). Five of the 39 patients (13%) were considered not evaluable for response because they stopped therapy within less than 1 month of starting it (3 patients for personal choice and 2 because of drug-related side effects); 34/39 patients (87%) were considered evaluable for response. The mean platelet count of the evaluable population prior to therapy was 1227×10^9/L (range 850-2390×10^9/L): of these 34 patients, 9 (26.5%) had a platelet count ≥ 1500×10^9/L.

Response

A response was observed in 32/39 patients (82%) in an intention-to-treat analysis and in 32/34 evaluable patients (94%). Fifteen of the 34 evaluable patients (44%) achieved a CR, with a reduction of platelet counts to less than 450×10^9/L, and 17/34 (50%) had a PR with platelet counts of 450-600×10^9/L (Figure 1). Among the 9 patients with a platelet count ≥1500×10^9/L before treatment, 6 had a CR and 2 had a PR. Response was reached in a median time of 4.2 months (range 0.2-12) using a mean daily dose of anagrelide of 2 mg (range 1–3, SD 0.62). The mean platelet count for all responding patients was 449×10^9/L (range 175-575×10^9/L) (Table 1). Two patients (6%) did not respond at all and stopped treatment after 7 and 8 months. All disease-related symptoms present before starting therapy disappeared in responding patients.

Maintenance therapy was given to all responders to keep platelet counts below a level considered to be safe (<600×10^9/L),[3,41,42] and is either still ongoing or had been continued until the last available measurement. The mean daily maintenance dose of anagrelide was 2 mg (range 1-3, SD 0.69). There was not a statistically significant difference between the mean daily dose given to achieve a response and the maintenance dose. The median follow-up time from the start of therapy to the last platelet measurement or to drug withdrawal, and the duration of therapy of all evaluable patients was 73 months (range 6-150). The median follow-up time and duration of therapy of responding patients (n=32) was 89.5 months (range 6-150).

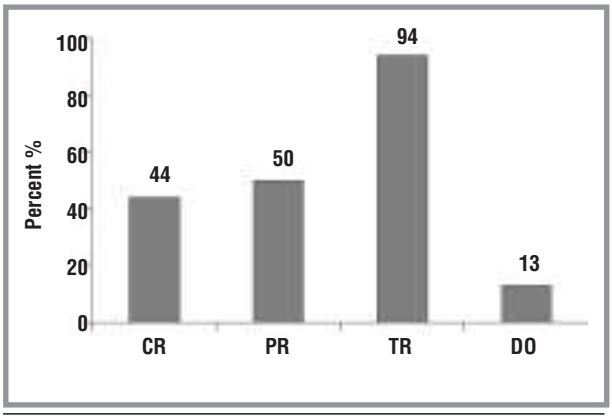

Figure 1. Outcome of enrolled patients. Thirty-nine patients were enrolled, 5 dropped out (DO), and of the 34 evaluable patients, 15/34 (44%) showed a complete response (CR) and 17/34 (50%) showed a partial response (PR), giving a total response (TR) rate of 94%.

Side effects

Every side effect, whether mild or severe (WHO classification of 0-4), was recorded. Side effects were observed in 20 out of 39 patients (51.3%) at a median time of 6 months (range 0.2-134) after starting therapy; 4 patients experienced two or more side effects. A total of 26 episodes were recorded: 14 during the initial course of therapy prior to reaching a response and 12 during maintenance therapy (Table 2). These side effects were tachycardia: 9 (35%); gastric distress: 6 (23%); anemia: 4 (15%); headache: 2 (7.7%); capillary leak syndrome: 2 (7.7%); acute fluid retention: 1 (3.8%); alopecia: 1 (3.8%); and cutaneous rash: 1 (3.8%). We compared daily doses of anagrelide at the occurrence of side effects, both during the course of initial therapy (mean 2.3 mg, SD 0.57) and during maintenance (mean 2 mg, SD 0.66), with those given at response (mean 2 mg, SD 0.62) and at maintenance (mean 2 mg, SD 0.69) of all responding patients: no statistically significant differences in dosages were seen.

Hemoglobin concentration was measured in all responding patients over the course of the study and as

Table 1. Platelet counts before treatment with anagrelide and at response to therapy.

	n (%)	*Mean platelet count n × 10⁹/L (range)*		*Median time to response*
		Before treatment	*At response*	*Months (range)*
All evaluable patients	34 (100)	1227 (850-2390)	–	–
Patients with CR	15 (44)	1150 (850-1860)	353 (175-448)	2 (0.2-12)
Patients with PR	17 (50)	1241 (856-2390)	535 (452-575)	5 (1-12)
All responding patients	32 (94)	1198 (850-2390)	449 (175-575)	4.2 (0.2-12)

part of their follow-up to monitor any possible development of anemia. Anemia, defined as a decrease of hemoglobin levels below 12 g/dL in females and below 13g/dL in males, appeared only during late follow-up in 4 responding patients on maintenance therapy (Table 3). Mild anemia (between 10-12 g/dL in females or between 10-13 g/dL in males) occurred in 1 patient, moderate anemia (between 8-10 g/dL) in 2, severe anemia (Hb ≤ 8g/dL) in one. At diagnosis, all 4 of these patients had hemoglobin levels within the normal range and bone marrow biopsies were consistent with a diagnosis of ET, megakaryocyte hyperplasia, and no fibrosis. Bone marrow biopsy performed when the anemia was detected showed a pattern of erythroblastic hypoplasia without fibrosis and involvement of other cell lines in the patient with Hb <8 g/dL, while the 2 patients with moderate anemia showed a pattern of myelofibrosis (stage II–III). Erythropoietin levels were increased in these 2 patients (120 mU/mL and 66 mU/mL, normal values 6-25) and moderately decreased in the patient with mild anemia (4.2 mU/mL). Reticulocyte counts were reduced in all 4 patients. Other possible causes of anemia (bleeding, hemolysis, hemoglobinopathies, deficiency of iron, folate or vitamin B12) were excluded. Anagrelide was stopped in 2 patients, 1 with moderate anemia and myelofibrosis and the other with severe anemia. The daily doses administered to the other 2 patients were reduced. The hemoglobin levels in the patient with severe anemia recovered within 3 months after discontinuing therapy. Stable hemoglobin values were maintained in the other patients who remained on therapy throughout the follow-up. Hemoglobin levels of all responding patients were analyzed by comparing values recorded at the onset of therapy (mean 13.6±1.31 g/dL; range 10.5-16.0 g/dL) with those recorded at response (mean 12.9 ± 1.36 g/dL; range 10.1-15.9 g/dL)

Table 2. Total side effects attributed to anagrelide, observed in 20/39 patients (51.3%) at a median time of 6 months after starting therapy (range 0.2-134); 4 patients experienced two or more side effects. No statistically significant differences were seen in the daily doses of anagrelide being administered when side effects occurred during the initial therapy or during response and maintenance.

Side Effect	*Episodes n (%)*	*Response CR/PR/NR/NE°*	*Median time elapsed between start of therapy and occurrence of side effects in months (range)*	*Mean daily dose at onset of side effects (mg)*
Tachycardia	9 (35)	2/7/0/0	6 (3-14)	2.50 (1.75-3)
Gastric distress	6 (23)	2/3/1/0	6 (0.2-23)	2.20 (1.75-3)
Anemia	4 (15)	0/4/0/0	120 (21-134)	1.60 (0.5-2.5)
Headache	2 (7.7)	1/0/0/1	1.25 (0.5-2)	1.75 (1.5-2)
Capillary leak syndrome	2 (7.7)	0/0/1/1	1.25 (0.5-2)	2.50 (2-3)
Acute fluid retention	1 (3.8)	1/0/0/0	6	1.50
Alopecia	1 (3.8)	1/0/0/0	13	2.50
Cutaneous rash	1 (3.8)	1/0/0/0	15	2.75
Total episodes	26			

°CR: complete response; PR: partial response; NR: no response; NE: not evaluable.

Table 3. Late onset of anemia occurred in 4/39 (10%) treated patients.

Patient Gender Age in yrs.	*Hb g/dL at start*	*Hb g/dL at event (WHO grade)*	*Follow-up in months*	*Anagrelide in mg/day*	*Reticulocytes $n\times10^9$/L*	*DAT*	*EPO levels in mU/mL*	*Outcome*
M, 52	13.6	7.9 (3)	21	2.5	12	Negative	–	Therapy stopped; recovery
F, 38	12.4	8.7 (2)	134	0.5	15	Negative	120	Therapy stopped; evidence of myelofibrosis
M, 26	12.8	11.6 (1)	112	2	18	Negative	4.2	Therapy ongoing
F, 38	12.2	9.4 (2)	128	1.5	17	Negative	66	Therapy ongoing; evidence of myelofibrosis

and at the last measurement (mean 12.3±1.74 g/dL; range 7.9-16.6 g/dL). A statistically significant difference was found (p= 0.02 and p=0.001, respectively).

Some patients on study discontinued therapy due to side effects, some initially and some later. Therapy was discontinued in a total of 9 patients (23%): 2 dropped out within 1 month of starting therapy, one each because of headache and capillary leak syndrome. Seven responding patients discontinued therapy during maintenance treatment, after a median follow-up of 21 months (range 6-134): 2 because of anemia, 2 because of tachycardia, and one each because of cutaneous rash, gastric distress, and acute fluid retention.

Adverse events

In spite of therapy, 3 out of 39 patients (7.7%) had serious adverse events (Table 4). One patient developed myocarditis and the other two patients experienced thrombotic events (silent myocardial infarction and myocardial ischemia) after a follow-up of 20, 84, and 62 months, respectively. The daily dose of anagrelide was 2.5, 2, and 0.5 mg and platelet counts were 297×10^9/L, 370×10^9/L, and 575×10^9/L, respectively. These 3 patients all responded to treatment and were receiving maintenance therapy. The myocarditis was diagnosed by examining a biopsy of myocardial tissue that showed a histologic profile consistent with toxic cardiomyopathy. Anagrelide was discontinued and recovery was demonstrated by a successive myocardial biopsy performed 3 months after stopping therapy. A clear correlation between drug administration and this event was not well established. Before the occurrence of myocarditis, serial evaluations of the patient's cardiac function at the beginning of and during anagrelide therapy had shown normal patterns and no other cardiovascular risk factors had been found. In the 2 other patients with silent myocardial infarction and myocardial ischemia, no thrombotic events had occurred before starting anagrelide therapy, although both had histories of high levels of cholesterol and triglycerides and both smoked. Congenital or acquired risk factors for thrombophilia were excluded. Therapy was discontinued in both patients.

Late follow-up

To date, no cases of leukemic transformation or neoplasia have been recorded; 2/39 patients have developed myelofibrosis (5%). These two patients had been previously treated with rIFN plus pipobroman and pipobroman plus HU. Myelofibrosis was found along with persisting anemia that occurred during late follow-up. Four responding patients chose to discontinue therapy, during maintenance, after 9, 15, 27, and 46 months of treatment at a mean daily dose of anagrelide of 2 mg (range 1.5-2.5) and with a platelet count $<600\times10^9$/L in all. Another responding patient was withdrawn from the study after a follow-up of 98 months because of scarce adhesion to the protocol. Overall, seven patients chose to discontinue treatment, mainly due to the difficulty in obtaining the supplies of the compassionate use drug (3 patients within less than 1 month of starting of therapy and 4 responders during maintenance treatment). At present, 17 patients remain on therapy with a median follow-up of 115 months (range 55-150). At the last evaluation their mean platelet count was 543×10^9/L (range 310-862×10^9/L).

Discussion

This study provides data on the long-term use of anagrelide in rather young patients with ET. A CR was seen in 44% of patients and a PR in 50%, giving a total response of 94% in 34 evaluable patients. This observed response rate is comparable to, or better than, that produced by other cytotoxic agents such as busulfan, pipobroman, HU,[4,11,18,43-45] or rIFN-α.[19,46-49] and was achieved with

Table 4. Status of 3/39 patients (7.7%) who experienced serious adverse events. All three were responders on maintenance treatment, but had to discontinue therapy.

Patient gender; Age at event in yrs.	*Event (WHO grade)*	*Follow-up in months*	*Platelet count $n\times10^9$/L*	*Anagrelide in mg/day*	*Outcome*
M, 34	Myocarditis (3)	20	297	2.50	Therapy stopped
M, 48	Silent myocardial infarction (4)	84	370	2.00	Therapy stopped
M, 57	Myocardial ischemia (3)	62	575	0.50	Therapy stopped

a mean daily dose of 2 mg, and a maximum daily dose of 3 mg. These dose levels are lower than those reported in previous studies.[20,21,38] Our therapy schedule, with a slowly escalated dose, was planned with the aim of reducing side effects during the initiation of therapy. This explains why the median time to achieve a response was just over 4 months, which is longer than the time reported by others.[20,21] However, maintenance therapy was always necessary to keep platelet counts at safe levels ($< 600\times10^9$/L), with a mean daily dose equivalent to that used to achieve a response.

Among the 39 recruited patients, 34 were evaluable and 17 remained on therapy for about 12.5 years. The overall safety findings for side effects due to treatment are consistent with the pharmacologic profile of anagrelide.[21,22,34,38,50]

The occurrence of anemia in late follow-up has been reported previously in ET patients. Our data seem to agree with previous results showing that the decrease in hemoglobin concentration is peculiar to late follow-up.[38] In fact, we found a statistically significant decrease of hemoglobin levels when comparing the values recorded at the onset of therapy with those at response and at the last measurement in responding patients (p=0.02 and p=0.001, respectively). It is still not clear why anagrelide causes a reduction of hemoglobin concentration, although many hypotheses have been put forward.[38]

Myelofibrosis as a late evolution of ET is not an unusual pattern. As previously reported, about 10% of patients with polycythemia vera or ET develop myelofibrosis after about 15 years, irrespective of therapy.[3] Our 2 cases with myelofibrosis had a very long follow-up and both had failed to benefit from previous treatment: one with rIFN-α plus pipobroman and the other with pipobroman and HU. However, bone marrow biopsies did not show significant fibrosis in these patients either at diagnosis or before starting anagrelide therapy.

In 2/39 treated patients (5%) thrombotic events occurred during maintenance therapy in late follow-up. This contrasts with the 20% rate of thrombotic events previously reported,[38] which was much higher than in our experience. No symptoms related to ET or thrombotic events were recorded prior to therapy in either of our two cases, but dyslipidemia and cigarette smoking, which are risk factors for thrombosis in ET,[51,52] had been noted in both. In these cases, platelet counts at the time of the event did not seem to correlate with the occurrence of the thrombosis. In fact, platelet counts were 370×10^9/L in one patient and 575×10^9/L in the other. Perhaps, prophylaxis with anti-platelet drugs in patients with cardiovascular risk factors could be added to avoid thrombotic events.

The myocarditis that developed in one patient could not be clearly explained. However, cardiac muscle fibers recovered after discontinuation of anagrelide. A toxic effect of the drug or other causes were not well established, although the patient was hospitalized in an intensive care coronary unit. It is clear that a careful heart function evaluation is imperative both before starting therapy and during follow-up in patients treated with anagrelide, as indicated in most studies on this drug.[21,53] Unlike Storen and Tefferi,[38] we recorded no bleeding episodes in our study.

It is well known that leukemic transformation may occur during the late follow-up of ET patients because this is one facet of the natural history of the disease. Leukemic transformation may occur in a small number of untreated patients[7] or may be due to treatment agents (radioactive phosphorus, alkylating agents, and HU).[28,29,54,55] There have been no cases of leukemic transformation among our patients so far. This is in accord with recent reports on large cohorts of patients treated with anagrelide.[56,57]

Of our 39 patients, 5 dropped out within the first month: 2 due to side effects and 3 by the patients' choice. Of the remaining 34 evaluable patients, 2 did not respond; of the 32 responding patients, 7 stopped therapy due to side effects, 3 due to serious adverse events, 4 due to difficulty in obtaining supplies of the drug, and 1 due to scarce adhesion to protocol, leaving 17 patients remaining on therapy. The finding that 50% of patients dropped out of treatment for various reasons is not unprecedented.[57]

Practice guidelines for the therapy of ET are now available[58] from the Italian Society of Hematology (SIE) and the two affiliated Societies (SIES and GITMO): the main

recommendations for platelet-lowering treatment are age over 60 years, history of major thrombotic or hemorrhagic events, and platelet count over 1500×10^9/L. Among patients with ET who are candidates for treatment, anagrelide is recommended by the above guidelines as first-line therapy in subjects younger than 60, with the exclusion of women of child-bearing potential and subjects aged 40-60 years with a history of major thrombotic events. Although only 9 out 34 evaluable patients were at high risk (platelet count more than 1500×10^9/L), from our own experience, we can confirm that anagrelide could be proposed as first-line therapy in younger people with ET who need treatment for their disease, with a caution against its use in patients with heart disturbances. A correct and careful approach to patients should include monitoring of heart function before and during treatment and accurate records of the occurrence and management of any adverse events.

Anagrelide is easy to handle and should offer a valuable alternative to other platelet-reducing agents: however, prospective randomized studies, in particular with HU, are warranted to evaluate the exact role of this drug. In a recent British trial,[59] high-risk ET patients were randomized to receive hydroxyurea plus aspirin or anagrelide plus aspirin. This study was closed at the end of 2003 because of an excess of adverse events in the anagrelide arm, including hemorrhages, thrombotic complications and myelofibrotic transformation. Final data from this study are not available at the time of writing this paper.

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