

Long-term use of anagrelide in young patients with essential thrombocythemia

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Anagrelide is a novel platelet-lowering agent that has recently been approved for use in essential thrombocythemia (ET) and related disorders. Short-term drug efficacy and toxicity data have previously been presented. The purpose of this study was to obtain additional information regarding long-term anagrelide use. This is a retrospective series of 35 young patients (17 to 48 years) with ET who received anagrelide treatment before 1992. Initial drug dosage ranged between 1 and 10 mg/d, and the median maintenance dosage was 2.5 mg/d. The overall initial response rate of 94% included 74% com-

plete remissions and 20% partial remissions. Of the 33 responding patients, 27 (82%) remained on anagrelide therapy for a median of 10.8 years (range, 7 to 15.5). Of these, 66% maintained a complete and 34% a partial remission over the study period. In general, the reporting of somatic side effects decreased over time, and anemia was the only new side effect that emerged after long-term therapy. Eight patients (24%) experienced a more than 3 g/dL decrease in hemoglobin level. Despite active therapy, 20% of the patients experienced a total of 10 thrombotic episodes, and a similar proportion

experienced major hemorrhagic events. All thrombohemorrhagic complications occurred at a platelet count of more than $400 \times 10^9/L$. It is concluded that long-term treatment of ET with anagrelide is associated with decreased reporting of initial side effects and the development of mild-to-moderate anemia. Complete normalization of platelet counts may be needed to minimize residual thrombohemorrhagic risk during therapy. (Blood. 2001; 97:863-866)

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Introduction

Essential thrombocythemia (ET) is currently classified, with polycythemia vera and agnogenic myeloid metaplasia, as a chronic myeloproliferative disorder. Among these 3 disorders, ET has the best prognosis, with the least propensity to undergo transformation to acute leukemia.¹ At present, specific therapy in ET minimizes morbidity from thrombohemorrhagic complications and has not altered survival.² In this regard, a single randomized study showed significant reduction in the incidence of thrombosis when high-risk patients were treated with hydroxyurea.³ In addition, other, nonrandomized studies have suggested a reduction in thrombotic episodes, with an adequate control of thrombocytosis in patients treated with ET.^{4,5} On the other hand, the incidence of thrombosis in low-risk patients with ET may not be high enough to warrant drug therapy.⁶ Therefore, cytoreductive treatment in ET is currently reserved for patients who are considered to be at high risk for thrombohemorrhagic complications.^{4,5,7-9}

Platelet-lowering agents currently used in ET include hydroxyurea,^{3,10,11} pipobroman,^{10,12,13} interferon alpha,¹⁴⁻¹⁶ busulfan,^{5,17,18} radiophosphorus,¹⁹⁻²¹ and the newest of the agents, anagrelide.²²⁻²⁸ Anagrelide is an oral imidazo-quinazoline derivative that was initially approved in the United States in 1997 for use in ET, and the treatment indications have since been expanded to include polycythemia vera and related disorders. The mechanism of action of anagrelide is not well defined but may involve drug interference with megakaryocyte maturation.^{29,30}

The short-term benefits and side effects of anagrelide are now well established.³¹ Control of thrombocytosis occurs in more than 80% of patients with ET and related disorders, independent of disease category and previous treatment history.²³ Reported side effects include headache, palpitations, fluid retention, diarrhea, and

nausea.³¹ However, there is as yet little information regarding long-term efficacy and toxicity in ET. We report here on a group of young patients with ET who began treatment with anagrelide before 1992. Our primary goals were to identify any unexpected long-term toxicity, to examine the natural history of the known short-term side effects, to assess the durability of response, to monitor thrombohemorrhagic events, and to define the circumstances under which these events occurred.

Patients, materials, and methods

The current study was approved by the Institutional Review Board of the Mayo Clinic. The study population included consecutive young patients (age younger than 50 years) who were selected from a retrospective series of all patients with ET who were seen at our institution and were started on anagrelide therapy before 1992. In this study, we investigated only young patients to minimize the confounding effects of age and underlying comorbid conditions on the long-term toxicity and antithrombotic activity of anagrelide. The diagnosis of ET had been made according to conventional criteria.³² To be eligible for evaluation, patients had to have responded to or been treated with anagrelide for a minimum of 4 weeks. There were no restrictions regarding prior cytoreductive therapy or thrombosis risk profile. Anagrelide was initially administered in doses of either 0.5 or 1.0 mg every 6 hours, with increases of 0.5 mg/d every 5 to 7 days as needed to decrease the platelet count to levels acceptable to the treating physician.

During the first several weeks of treatment with anagrelide, initial side effects and the platelet count were closely monitored at least every 2 weeks. Once proper dose titration had been achieved, information on drug dosage, toxicity, and treatment efficacy was accumulated by reviewing progress

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Table 1. Incidence of reported side effects of anagrelide in 35 young patients with essential thrombocythemia during the first 3 months of treatment (initial) and afterward (long term)

	Headache	Tachycardia	Edema	Diarrhea
Initial	34.2%	22.8%	14.2%	8.5%
Long term	5.7%	8.5%	5.7%	0%

notes from periodic visits to our institution or by communication with the local primary physicians as well as with the patients themselves. For patients reporting thrombohemorrhagic complications, documentation as to the circumstances and details surrounding those events were obtained from the treating physicians. Thrombotic episodes other than superficial thrombophlebitis were considered major. Brief epistaxis, nonextensive ecchymoses, and gingival hemorrhage were considered minor bleeding events. Side effects that were reported in the first 3 months of anagrelide therapy were considered short-term or initial, whereas those that continued to be reported after the first 3 months of treatment constituted long-term side effects. In addition to somatic complaints, pretreatment and posttreatment (most recent) hemoglobin levels were recorded and compared by the Wilcoxon signed-rank test. Complete response was defined as a sustained platelet count of less than $450 \times 10^9/L$. Partial response was defined as a platelet count of between 450 and $600 \times 10^9/L$ or a 50% reduction from baseline.

Results

Clinical characteristics

We identified 35 young patients with ET who were started on anagrelide therapy before 1992. The median age of the group was 38 years (range, 17 to 48). Before treatment with anagrelide, 77% of the patients (27 cases) had symptomatic disease, including a history of thrombosis in 20%, hemorrhage in 26%, and vasomotor manifestations in 51%. Twenty-four patients (69%) had previously been treated with either hydroxyurea or busulfan. The median platelet count at the start of anagrelide therapy was $1075 \times 10^9/L$ (range, 690 to 2525). The median starting dose of anagrelide was 2.0 mg/d (range, 1 to 10), with a median maintenance dosage of 2.5 mg/d (range, 1 to 5).

Treatment response

Follow-up information was available for all the patients over the duration of the study. The overall initial response rate was 94.3%, with 26 patients (74.3%) achieving complete remission, 7 (20%) having partial remission, and only 2 (5.7%) showing no response. Over the duration of the study, 27 of the 33 responding patients (82%) remained on anagrelide therapy for a median of 10.8 years (range, 7 to 15.5). Of the 6 initially responding patients who are currently not on therapy, 2 died while on therapy, one from a basilar

Table 2. Thrombotic events that occurred in 7 of 35 young patients who were treated with anagrelide and followed for up to 15.5 years

Patient	Event	Platelet count at time of event ($\times 10^9/L$)
1	Cerebrovascular accident	1578
2	Transient ischemic attack	688
3	Deep vein thrombosis	571
4	Thrombophlebitis	424
5	Thrombophlebitis	682
6	Thrombophlebitis	618
7	Cerebrovascular accident	900
	Deep vein thrombosis	600
	Deep vein thrombosis	751
	Pulmonary embolism	973

artery hemorrhage and one from a motor vehicle accident. The remaining 4 patients withdrew from anagrelide therapy because of either side effects (3 patients) or progressive splenomegaly (one patient). Of the 29 patients who responded and did not withdraw from treatment because of side effects, 19 (66%) maintained complete remission and 10 (34%) partial remission during the treatment course. Six of the 10 patients with partial remission had initially achieved complete remission. In 3 of these, the dosage of anagrelide had to be reduced because of side effects, and the other 3 lost their complete remission without a change in dosage.

Toxicity

The initial side-effect profile of anagrelide in our patients was similar to that described in previous short-term studies (Table 1). Over the long term, anemia was the only new side effect that emerged. Pretreatment hemoglobin (median, 13.5 g/dL, range, 11.4 to 15.9) and posttreatment hemoglobin (median, 12.3 g/dL, range, 8.9 to 16.1) levels were available in 33 of the 35 patients and showed a significant difference ($P < .0001$). Eight patients (24%) had a more than 3 g/dL reduction in hemoglobin level. On the other hand, reporting by patients of the known side effects decreased over time (Table 1). Side effects resulted in discontinuation of treatment in 3 cases after 2 months (headaches), 7 months (headaches, diarrhea, edema), and 12 months (nausea) of treatment with anagrelide. In addition, dosage reductions because of somatic side effects were documented in 3 patients, one for tachycardia, one for edema, and one for edema and headache.

Thrombohemorrhagic events during treatment with anagrelide

Seven patients (20%) experienced a total of 10 episodes of thrombosis over the duration of the study (Table 2). The platelet count during the adverse episodes was above $400 \times 10^9/L$ in all the cases, and above $600 \times 10^9/L$ in 8 of the 10 total episodes. None of the events were fatal. Seven patients (20%) experienced major hemorrhagic events over the duration of the study (Table 3). The complication was fatal in the patient who had basilar artery hemorrhage. Similar to the circumstances surrounding the thrombotic complications, the platelet count during the bleeding episodes was always more than $400 \times 10^9/L$. In total, 4 major thrombohemorrhagic events occurred despite platelet counts of 400 to $600 \times 10^9/L$. In addition, one episode of thrombophlebitis and 3 minor episodes of epistaxis were reported at a median platelet count of $550 \times 10^9/L$.

Discussion

Because of the expectedly long survival of patients with ET, it is imperative that specific treatment be both well tolerated and efficacious over the long term. Before the recent introduction of

Table 3. Hemorrhagic events that occurred in 7 of 35 young patients who were treated with anagrelide and followed for up to 15.5 years

Patient	Event	Platelet count at time of event ($\times 10^9/L$)
1	Gastrointestinal bleeding	911
2	Gastrointestinal bleeding	924
3	Gastrointestinal bleeding	409
4	Retinal artery hemorrhage	412
5	Basilar artery hemorrhage	453
6	Uterine hemorrhage	680
7	Pulmonary hemorrhage	647

anagrelide as a platelet-lowering agent in chronic myeloproliferative disorders,²³ patients with ET had been treated with hydroxyurea, alkylating agents, and radioactive phosphorus. Each of these modalities, however, is potentially leukemogenic.^{10,33-35} This particular concern has encouraged the investigation of presumably nonleukemogenic treatment agents, including interferon alfa and anagrelide.³⁶ The present long-term study complements the preliminary treatment reports of anagrelide therapy in ET by describing the natural history of the initial drug side effects, the possible emergence of new side effects, the durability of initial responses, and the clinical efficacy of maintenance therapy. To minimize the confounding effect of advanced age and comorbid conditions on these objectives, the study was restricted to young patients.

The spectrum and incidence of initial side effects of anagrelide therapy in our study population were similar to those described in the original studies.^{22,23} With a dropout rate due to side effects of only 9% and the demonstration of decreased reporting of side effects over time, this study suggests long-term tolerability of anagrelide in ET. The possible development of tolerance to initial side effects has also been implied by other studies.^{27,28} No new somatic side effects emerged after a median treatment period of approximately 11 years. However, the number of patients in the current study was too small to allow accurate assessment of the occurrence of rare side effects such as congestive heart failure.²³ However, we are not aware of the reporting of any somatic side effects of anagrelide that had not previously been described.

During the original anagrelide studies, the median hemoglobin level decreased by 1 g/dL after approximately 2 years of treatment.²³ The results from the current study are similar and suggest that a longer treatment period may result in further deterioration of anemia. The reduction in the pretreatment level of hemoglobin by more than 3 g/dL in almost a quarter of the patients on treatment was impressive. The pathogenesis of anagrelide-induced anemia is not known. In previous *in vitro* studies, we and others have shown that anagrelide does not significantly affect erythroid and granulocyte progenitor growth and that only supratherapeutic concentrations inhibit megakaryocyte proliferation.^{22,29,30} On the other hand, the use of other quinazoline derivatives has been associated with a marked decrease in serum erythropoietin concentration in patients with posttransplant erythrocytosis.³⁷ Whether anagrelide alters the endogenous synthesis or erythroid precursor sensitivity of erythropoietin remains to be determined. However, erythropoiesis in ET may not always be erythropoietin dependent.^{38,39} Regardless, we have occasionally observed improvement in anemia in some patients who are either taken off anagrelide treatment or were concomitantly treated with exogenous administration of erythropoi-

etin. In any case, hemodilution from fluid retention may contribute to the anemia in some patients on anagrelide therapy.

The majority of the patients (54%) achieved and sustained a complete remission (platelet count less than $450 \times 10^9/L$) over a median of approximately 11 years of treatment with anagrelide. However, a substantial minority (29%) were in partial remission over the long term and their clinical course was interrupted by major thrombotic and hemorrhagic events, each occurring in 20% of the total study population. Of note, only 2 of the 7 patients with thrombotic events had a history of thrombosis, and inadequately controlled thrombocytosis was also prevalent in the patients who experienced minor bleeding episodes. These observations are consistent with those of previous reports associating a substantial risk of thrombosis with mild-to-moderate thrombocytosis (platelet count 400 to $600 \times 10^9/L$).^{4,5,40} In one particular study, for example, all hemorrhagic events occurred at platelet counts of 500 to $650 \times 10^9/L$, and the overall risk of severe disease complications was 22% versus 4% at platelet levels of less than 600 compared with $400 \times 10^9/L$.⁴⁰ Similarly, in a randomized study of high-risk patients comparing hydroxyurea treatment with no treatment, the only 2 thrombotic events that occurred in hydroxyurea-treated patients were associated with platelet counts of 490 and $632 \times 10^9/L$.³ Therefore, it is possible that the residual risk of thrombosis in treated patients with ET can be further decreased by keeping the platelet count below $400 \times 10^9/L$. It is underscored, however, that the target platelet count in patients with ET requiring treatment needs to be addressed in a prospective randomized setting.

Large, randomized studies are needed to accurately compare the efficacy and toxicity of platelet-lowering agents in ET. Controlled studies are also needed to separate inherent disease characteristics from treatment-induced events. In the current study, we have shown long-term tolerability of anagrelide therapy in ET. Although this was comforting, we were impressed by the continued occurrence of thrombohemorrhagic events, despite active therapy. A careful analysis of patient data suggests that the aggressive control of thrombocytosis to a platelet count of less than $400 \times 10^9/L$ may be imperative to minimize the incidence of recurrent thrombohemorrhagic events, regardless of the treatment agent used. However, the occurrence of dose-dependent side effects may not allow the optimal use of a specific agent and require the use of an alternative agent. The latter situation may be more relevant to an older patient population, to whom the results of this study cannot be extrapolated.

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