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

Elizabeth C. Storen and Ayalew Tefferi

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% complete 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 x 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)

© 2001 by The American Society of Hematology

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. Our primary goals were to identify any unexpected short-term side effects, to assess the durability of response, to monitor thrombohemorrhagic events, and to define the circumstances under which these events occurred.

© 2001 by The American Society of Hematology
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, nonextension 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 × 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 × 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 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 × 10^9/L in all the cases, and above 600 × 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 × 10^9/L. In total, 4 major thrombohemorrhagic events occurred despite platelet counts of 400 to 600 × 10^9/L. In addition, one episode of thrombophlebitis and 3 minor episodes of epistaxis were reported at a median platelet count of 550 × 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 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)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Platelet count at time of event (× 10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cerebrovascular accident</td>
<td>1578</td>
</tr>
<tr>
<td>2</td>
<td>Transient ischemic attack</td>
<td>688</td>
</tr>
<tr>
<td>3</td>
<td>Deep vein thrombosis</td>
<td>571</td>
</tr>
<tr>
<td>4</td>
<td>Thrombophlebitis</td>
<td>424</td>
</tr>
<tr>
<td>5</td>
<td>Thrombophlebitis</td>
<td>682</td>
</tr>
<tr>
<td>6</td>
<td>Thrombophlebitis</td>
<td>618</td>
</tr>
<tr>
<td>7</td>
<td>Cerebrovascular accident</td>
<td>900</td>
</tr>
</tbody>
</table>

### 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

<table>
<thead>
<tr>
<th>Patient</th>
<th>Event</th>
<th>Platelet count at time of event (× 10^9/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Gastrointestinal bleeding</td>
<td>911</td>
</tr>
<tr>
<td>2</td>
<td>Gastrointestinal bleeding</td>
<td>924</td>
</tr>
<tr>
<td>3</td>
<td>Gastrointestinal bleeding</td>
<td>409</td>
</tr>
<tr>
<td>4</td>
<td>Retinal artery hemorrhage</td>
<td>412</td>
</tr>
<tr>
<td>5</td>
<td>Basilar artery hemorrhage</td>
<td>453</td>
</tr>
<tr>
<td>6</td>
<td>Uterine hemorrhage</td>
<td>680</td>
</tr>
<tr>
<td>7</td>
<td>Pulmonary hemorrhage</td>
<td>647</td>
</tr>
</tbody>
</table>
anagrelide as a platelet-lowering agent in chronic myeloprolifera-
tive disorders, patients with ET had been treated with hydroxy-
urea, alkylating agents, and radioactive phosphorus. Each of these
modalities, however, is potentially leukemogenic. This par-
ticle concern has encouraged the investigation of presumably
nonleukemogenic treatment agents, including interferon alfa and
anagrelide.

The present long-term study complements the prelimi-
nary 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. 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. 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.
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 treat-
ment. 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 granulo-
cyte progenitor growth and that only superatherapeutic concen-
trations inhibit megakaryocyte proliferation. 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. Whether anagrelide alters the
endogenous synthesis or erythroid precursor sensitivity of erythro-
poietin remains to be determined. However, erythrocytosis in ET
may not always be erythropoietin dependent.

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). 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 complica-
tions was 22% versus 4% at platelet levels of less than 600
compared with 400 \times 10^9/L. Similarly, in a randomized study of
high-risk patients comparing hydroxyurea treatment with no treat-
ment, the only 2 thrombotic events that occurred in hydroxyurea-
treated patients were associated with platelet counts of 490 and
632 \times 10^9/L. 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 impres-
sed 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.

References

1. Rozman C, Giralt M, Felu E, Rubio D, Cortes MT. Life expectancy of patients with chronic nonleu-
2. Toffere A, Solberg LA Jr, Silverstein MN. A clinical update in polycythemia vera and essential thrombocy-
thrombocythemia: a study of the predictive factors in a se-
5. Bussu C, Varela E, Pereira A, et al. Major vascular complications in essential thrombocy-
themia: a study of the predictive factors in a se-
6. Fenaux P, Simon M, Cauiller MT, Lai JL, Goude-
mand J, Bauters F. Clinical course of essential
thrombocythemia in 147 cases. Cancer. 1990;66:
545-556.
7. Ruggeri M, Finazzi G, Tosetto A, Riva S, Ro-
deghiero F, Barbui T. No treatment for low-risk
themia: clinical evolutionary and bio-
myeloid leukemia and myelodysplastic syn-
dromes following essential thrombocythemia
with hydroxyurea: high proportion of cases
myeloid leukemia and myelodysplastic syn-
dromes following essential thrombocythemia
with hydroxyurea: high proportion of cases
11. Lofvenberg E, Whalin A. Management of poly-
cythemia vera, essential thrombocythemia and
1988;41:375-381.
13. Brusamolino E, Canevari A, Salvanesci L, Mer-
ante S, Bernasconi C. Efficacy trial of pipobro-
man in essential thrombocythemia: a study of 24
pha-2b in the long-term treatment of essential
Long-term use of anagrelide in young patients with essential thrombocythemia

Elizabeth C. Storen and Ayalew Tefferi