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ORIGINAL ARTICLE

Comparison of starting doses of anagrelide as a first-line therapy in patients with cytoreductive therapy-naïve essential thrombocythemia: difference between starting at 0.5 and 1.0 mg/day

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Abstract

Anagrelide is widely used for cytoreductive therapy in patients with essential thrombocythemia who are at high risk for thrombosis. The recommended starting dose in the package insert of anagrelide varies by country. A high starting dose leads to an early onset of action, but causes a higher incidence of adverse events. This relationship indicates that both the onset of action and side effects of anagrelide are dose dependent. We retrospectively compared the efficacy and safety of anagrelide as a first-line drug between patients with essential thrombocythemia who started at 0.5 or 1.0 mg/day. Incidence of total adverse events and anagrelide-related palpitation, discontinuation rates, and the median daily dose of anagrelide were lower in the 0.5 mg/day group than in the 1.0 mg/day group; however, comparable platelet-lowering effects were achieved in both groups. These data suggest that a low starting dose of anagrelide followed by dose escalation may result in fewer adverse events and lower discontinuation rates, while providing desirable platelet-lowering effects. Initiating anagrelide at a lower dose may be a useful approach in actual clinical practice.

Keywords Essential thrombocythemia · Anagrelide · First line · Starting dose

Introduction

Patients with essential thrombocythemia (ET) have shorter life expectancies than age- and gender-matched individuals of the general population [1], with approximately 10–20% of patients developing thrombosis after diagnosis [2–4]. The treatment goals for ET are preventing the onset of thrombo-hemorrhagic events (THEs), progression to myelofibrosis (MF), or acute leukemia (AL), as well as the development of secondary cancer. In patients at high risk for thrombosis, many guidelines recommend antiplatelet and cytoreductive therapy [5–7]. As first-line drugs for cytoreductive therapy, hydroxyurea and anagrelide are recommended by Japanese clinical practice guidelines [5], and hydroxyurea and recombinant interferon-alpha (rIFNα) have been recommended by the European LeukemiaNet (ELN) [6]. For patients with inadequate response/intolerance to hydroxyurea in the first-line setting, anagrelide and rIFNα are recommended as second-line drugs. According to the National Comprehensive Cancer Network (NCCN) guidelines [7], hydroxyurea, IFNs, and anagrelide are recommended as

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first-line drugs at the same therapeutic level. Therefore, the recommended first-line drugs for cytoreductive therapy vary to some extent depending on their approval status in each country. Anagrelide is a unique drug because it was originally developed as a new antiplatelet agent owing to its inhibitory action on phosphodiesterase III activity. However, it later became better known for its platelet-lowering effect via low-dose administration [8, 9]. Although anagrelide has been suggested to inhibit both megakaryocyte maturation and proplatelet formation [10] and selectively inhibit the expression of transcription factors in megakaryocytic proliferation [11, 12], its mechanism of action has not been fully elucidated. The platelet-lowering effect and adverse events of anagrelide are considered dose dependent [13]. According to reports published during the beginning phase of its clinical application when the starting dose was high ($\geq$ 1.5 mg/day), the response rates were good, but adverse events were frequent [14, 15]. Although the current recommended starting dose of anagrelide in the package insert is 1.0 mg/day in Japan and Europe, it is 2.0 mg/day for adults and 0.5 mg/day for children in the United States. Thus, it is possible that responsiveness to the drug varies depending on the race and physical constitution. We have recently reported real-world data on the usefulness and safety of anagrelide as a first-line drug in Japan and observed that 60.4% of patients experienced treatment-related adverse events [16]. Another previous study in Japan found that 93% of patients experienced treatment-related adverse events [17], which are a key reason for anagrelide discontinuation in clinical practice. Therefore, avoiding treatment discontinuation because of anagrelide-related side effects is important.

This study was a post hoc analysis of previously reported data, which were retrospectively analyzed to compare the efficacy and safety of anagrelide between patients who started on a dose of 0.5 or 1.0 mg/day.

Materials and methods

Patients

Although details have been described previously [16], this study was a retrospective study involving 53 patients with ET (31 patients at Kansai Medical University, 16 patients at Tottori Prefectural Central Hospital, and six patients at Kobe City Nishi-Kobe Medical Center) who received anagrelide as a first-line drug for cytoreductive therapy. Based on medical records, the following data were obtained: patient characteristics, history of THEs, cardiovascular risk factors (defined as diabetes mellitus, hypertension, high low-density lipoprotein cholesterolemia, hyperlipidemia, and/or smoking), status of antiplatelet therapy or anagrelide treatment, concomitant use of other cytoreductive therapies, therapeutic effects, adverse events, and onset of THEs after diagnosis, or transformation to MF or AL, occurrence of secondary cancer, and cause of death after anagrelide administration. This study was conducted with the approval of the ethics review committees of Kansai Medical University, Tottori Prefectural Central Hospital, and Kobe City Nishi-Kobe Medical Center.

Treatment

Anagrelide was started at 0.5 or 1.0 mg/day at the discretion of the attending physicians, and the dose was increased according to the package insert until efficacy was achieved at the lowest possible dose. When it was difficult to continue treatment or increase the dose because of inadequate response or adverse events during anagrelide monotherapy, hydroxyurea was administered as a second-line drug, either switched from or added to anagrelide at the discretion of the attending physicians. In accordance with the Japanese clinical practice guidelines [5], the antiplatelet agents were administered to patients at high risk for thrombosis and those at low risk for thrombosis with cardiovascular risk factors or *JAK2* mutations. However, this administration did not apply if the patient refused this course of treatment.

Definition

We used the World Health Organization classifications 2008 [18] and 2017 [19] for the diagnostic criteria of ET. The thrombosis risk category was stratified in accordance with the following major risk classifications: conventional risk classification [20], International Prognostic Score of Thrombosis for Essential Thrombocythemia (IPSET-thrombosis) [21], and revised IPSET-thrombosis [22]. Regarding THEs, thrombotic events were defined as stroke, transient ischemic attacks (TIAs), myocardial infarction, angina pectoris, peripheral arterial obstructive disease, erythromelalgia, deep vein thrombosis, and pulmonary embolism, and hemorrhagic events were defined as cerebral hemorrhage, gastrointestinal hemorrhage, hematuria, and mucosal hemorrhage. The therapeutic effect of cytoreductive therapy was evaluated according to the ELN criteria [20], and adverse events were classified according to the Common Terminology Criteria for Adverse Events version 4.0. Secondary malignancies were defined as new malignancies that occurred during the observation period regardless of the use of drugs. For MPN gene mutation analysis, polymorphonuclear leukocytes were isolated from blood samples. The presence or absence of *JAK2V617F* and *MPL-W515L/K* mutations was assessed using DNA extraction and allele-specific polymerase chain reaction (PCR). With respect to the exon nine region in *CALR* genes, the presence or absence of a mutation was confirmed using PCR or the direct sequencing method.

Statistical analysis

Regarding the analysis set, the characteristics, treatment status, adverse events, occurrence of THEs, and other information were described [16]. Fisher's exact test was used for nominal variables, and Mann–Whitney *U* test was used for continuous variables. All statistical analyses of valid variables were performed using two-sided tests, and $P < 0.05$ was considered statistically significant. Statistical analysis was performed using the EZR (Easy R) software [23] and GraphPad Prism (GraphPad Software).

Results

The characteristics of 53 subjects (22 men and 31 women) are shown in Table 1. Anagrelide was started at 0.5 mg/day in 21 patients (39.6%) (group A) and at 1.0 mg/day in 32 patients (60.4%) (group B). Although no significant differences were observed regarding major patient characteristics at the time of diagnosis between the two groups, the percentage of *CALR* mutations in group A and the percentage of *JAK2* mutations in group B tended to be slightly higher. All six patients with a history of heart failure (all categorized as New York Heart Association Functional Classification Class I) were in group B. Based on the conventional thrombotic risk classification, there were 12 low-risk patients and 41 high-risk patients at the time of diagnosis (Suppl. Table 1). Before the start of anagrelide therapy, four patients were ≥ 60 years of age, and 8 and 45 patients were deemed to have low and high risk, respectively (Table 2). Among the low-risk patients, three had a platelet count of $\geq 1000 \times 10^9$/L prior to the start of anagrelide treatment, and the other four were *JAK2* mutation-positive. Based on the IPSET-thrombosis score, there were 11 low-risk, seven intermediate-risk, and 35 high-risk patients at the time just before starting anagrelide (Table 2). Based on the revised IPSET-thrombosis score, they were classified into three very low risk, eight low risk, 10 intermediate risk, and 32 high risk. There were no significant differences between Group A and Group B with these risk classification scores (Table 2). Similarly, in these scores at the time of diagnosis, there were no significant differences between group A and group B (Suppl. Table 1).

In all 53 patients, the median duration of anagrelide treatment was 642 days (range 43–1219 days); the median daily dose was 1.44 mg/day (range 0.53–2.78 mg/day); the rate of achieving a platelet count $< 600 \times 10^9$/L during anagrelide monotherapy was 83.0% (44 patients); the median time to the achievement of a platelet count $< 600 \times 10^9$/L was 53 days; and the best response achieved was complete response (CR) in 27 patients (50.9%), partial response (PR) in 18 patients (34.0%), and no response in 8 patients (15.1%) (Table 3). The platelet count before starting anagrelide therapy tended to be higher in Group B, albeit without significance. Although the possible influence of the elevated platelet count in group B cannot be eliminated, the median daily dose was significantly lower ($P = 0.021$) in group A (1.37 mg/day [range 0.58–2.32 mg/day]) than in group B

Table 1 Characteristics of all patients and each group by starting dose of anagrelide

Patients characteristics at diagnosis	Total ($n = 53$)	Group A 0.5 mg/day start ($n = 21$)	Group B 1.0 mg/day start ($n = 32$)	A vs. B *P* value
Age, median (range)	67.0 (21–93)	67.0 (36–93)	66.5 (21–83)	0.682
Male, *n* (%)	22 (41.5)	7 (33.3)	15 (46.9)	0.400
Female, *n* (%)	31 (58.5)	14 (66.7)	17 (53.1)	0.400
Body weight, median; kg (range)	53.0 (38.0–84.0)	52.0 (40.0–84.0)	54.5 (38.0–72.0)	0.643
WBC, median; $\times 10^9$/L (range)	9.5 (5.7–20.5)	9.1 (5.7–13.4)	10.0 (5.7–20.5)	0.131
Neutrophil rate, median; % (range)	71.4 (54.7–87.0)	71.0 (54.7–87.0)	71.7 (56.0–83.0)	0.891
Hb, median; g/dL (range)	14.2 (8.6–19.0)	13.6 (9.6–19.0)	14.2 (8.6–18.4)	0.248
Plt, median; $\times 10^9$/L (range)	913 (514–2453)	872 (605–2453)	936 (514–1784)	0.534
LDH, median IU/L (range)	237 (171–631)	227 (172–589)	260 (171–631)	0.928
JAK2 gene mutation, *n* (%)	34 (64.2)	11 (52.8)	23 (71.9)	0.241
CALR gene mutation, *n* (%)	11 (20.8)	6 (28.6)	5 (15.6)	0.310
MPL gene mutation, *n* (%)	1 (1.9)	1 (4.8)	0	NA
Triple-negative, *n* (%)	7 (13.2)	3 (14.3)	4 (12.5)	NA
History of thrombosis, *n* (%)	17 (32.1)	8 (38.1)	9 (28.1)	0.551
Cardiovascular risk factors, *n* (%)	29 (54.7)	11 (52.4)	18 (56.3)	> 0.999
Cardiac failure, *n* (%)	6 (11.3)	0	6 (18.8)	0.070
Antiplatelet medications, *n* (%)	28 (52.8)	10 (47.6)	18 (56.3)	0.584

NA not analyzed

Table 2 Risk classification of all patients and each group by starting dose of anagrelide before the start of anagrelide therapy

Risk classification	Total ($n=53$)	Group A 0.5 mg/day start ($n=21$)	Group B 1.0 mg/day start ($n=32$)	A vs. B *P* value
Conventional risk classification				
Low	8	3	5	0.907
High	45	18	27	0.907
IPSET-thrombosis score				
Low	11	5	6	0.669
Intermediate	7	3	4	0.865
High	35	13	22	0.618
Revised IPSET-thrombosis score				
Very low	3	2	1	0.340
Low	8	2	6	0.371
Intermediate	10	5	5	0.469
High	32	12	20	0.707

IPSET-thrombosis International prognostic score of thrombosis for essential thrombocythemia

Table 3 Details of treatment and response

Treatment and response	Total ($n=53$)	Group A 0.5 mg/day start ($n=21$)	Group B 1.0 mg/day start ($n=32$)	A vs. B *P* value
Plt before starting anagrelide, median; $\times 10^9$/L (range)	965 (605–2453)	872 (605–2453)	1083 (618–1636)	0.089
Duration of anagrelide therapy, days				
Mean (SD)	656 (378)	701 (328)	627 (362)	
Median (range)	642 (43–1219)	708 (169–1219)	574 (43–1206)	0.422
Daily anagrelide dose, mg/day				
Mean (SD)	1.46 (0.48)	1.29 (0.35)	1.57 (0.52)	
Median (range)	1.44 (0.53–2.78)	1.37 (0.58–2.32)	1.49 (0.53–2.78)	0.021
Response (anagrelide monotherapy)				
Number of achieved a Plt count $<600\times10^9$/L, *n* (%)	44 (83.0)	17 (81.0)	27 (84.4)	>0.999
Complete response, *n* (%)	27 (50.9)	9 (42.9)	18 (56.3)	0.406
Partial response, *n* (%)	18 (34.0)	9 (42.9)	9 (28.1)	0.375
No response, *n* (%)	8 (15.1)	3 (14.3)	5 (15.6)	>0.999
Time between the start of anagrelide therapy and achievement of Plt count $<600\times10^9$/L, median (range)	54 (13–638)	42 (14–638)	56 (13–637)	0.562
Switch from anagrelide to hydroxyurea, *n* (%)	8 (15.1)	0	8 (25.0)	0.016
Addition of hydroxyurea to anagrelide, *n* (%)	9 (17.0)	3 (14.3)	6 (18.8)	>0.999
Discontinued anagrelide, *n* (%)	12 (22.6)	1 (4.8)	11 (34.4)	0.017

SD standard deviation

(1.49 mg/day [range 0.53–2.78 mg/day]). However, the rate of patients who achieved a platelet count $<600\times10^9$/L and the response rates were comparable between the two groups. Overall, hydroxyurea was used in 17 patients. These patients consisted of eight patients who switched from anagrelide to hydroxyurea (because of adverse events in four patients, transient response followed by reduced efficacy in three patients, and a thrombotic event in one patient) and nine patients who concomitantly used hydroxyurea with anagrelide (all because of inadequate response). In Group A, no patients switched to hydroxyurea, but three patients concomitantly used hydroxyurea. The number of patients who switched from anagrelide to hydroxyurea was significantly higher ($P=0.016$) in group B. Figure 1 shows the changes in the median platelet count between before and after anagrelide treatment in groups A and B. Both groups had a favorable course in terms of the platelet-lowering effect.

The observed adverse events and THEs are shown in Table 4. The median observation period was 4.1 years. Treatment-related adverse events were observed in 32 patients (60.4%), with the incidence being significantly

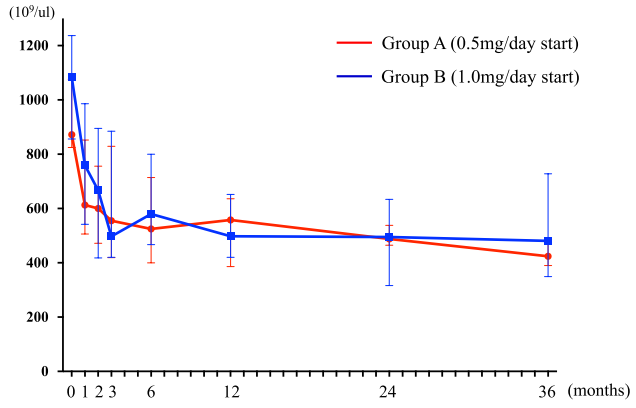

Fig. 1 Changes in the median platelet count before and after anagrelide treatment in groups A (starting dose of 0.5 mg/day) and B (starting dose of 1.0 mg/day). Both groups had a favorable course in terms of the platelet-lowering effect. Data are shown as median platelet counts ± quartiles. The median platelet counts immediately before and at 1, 2, 3, 6, 12, 24, and 36 months after the initiation of anagrelide therapy were 872×10^9/L, 613×10^9/L, 600×10^9/L, 555×10^9/L, 525×10^9/L, 558×10^9/L, 488×10^9/L, and 424×10^9/L, respectively, in group A, versus 1083×10^9/L, 759×10^9/L, 667×10^9/L, 497×10^9/L, 580×10^9/L, 498×10^9/L, 495×10^9/L, and 481×10^9/L, respectively, in group B

higher ($P=0.002$) in group B (78.1%; 25/32 patients) than in group A (33.3%; 7/21 patients). Of the total 47 adverse events observed, 43 were grade 1–2 events, whereas four were grade 3 events. Regarding frequently observed adverse events (palpitations in 14 patients [26.4%], headache in 11 patients [20.8%)], and anemia in 10 patients [18.9%]), group A had a significantly lower incidence of palpitations. Among the six patients with heart failure who started anagrelide at 1.0 mg/day, cardiac adverse events were observed in five patients, consisting of grade 3 heart failure in two patients, grade 3 and grade 2 anemia in one patient each, and grade 1 lower limb edema in one patient. During the observation period, 12 patients (22.6%) developed THEs. Thrombotic events occurred in eight patients (15.1%; 3.7/100 patient-years; cerebral infarction in three patients, TIA in one patient, myocardial infarction in three patients, and angina pectoris in one patient), and hemorrhagic events occurred in four patients (7.5%; 1.8/100 patient-years; hematuria in one patient, bloody sputum in one patient, and epistaxis in two patients). Disease transformation was observed in three patients, with all three cases attributable to MF. No significant differences were noted regarding the onset of THEs or disease transformation between the two groups. Twelve patients (22.6%) discontinued anagrelide (reported adverse events in five patients [9.4%], insufficient response in four patients [7.5%], thrombotic event in one patient, progression to MF in one patient, and death in one patient). Anagrelide was discontinued in one patient in group A, versus 11 patients in group B ($P=0.017$; Table 3).

Discussion

Although several prospective and retrospective studies have been conducted [13–17, 24–39], only a few have reported the use of anagrelide as a first-line drug in patients with ET, and the largest dataset was analyzed only in the prospective ANAHYDRET study [36]. In these reports, the starting dose

Table 4 Adverse events and development of thrombohemorrhagic events and transformation during anagrelide therapy

AEs, THEs and transformation	Total ($n=53$)	Group A 0.5 mg/day start ($n=21$)	Group B 1.0 mg/day start ($n=32$)	A vs. B P value
Number of patients with AEs	32 (60.4)	7 (33.3)	25 (78.1)	0.002
AEs (all grades)	47	7	40	
Palpitations, *n* (%)	14 (26.4)	0	14 (43.8)	< 0.001
Headache, *n* (%)	11 (20.8)	3 (14.3)	8 (25.0)	0.494
Anemia, *n* (%)	10 (18.9)	4 (19.0)	6 (18.8)	> 0.999
Diarrhea, *n* (%)	4 (7.5)	0	4 (12.5)	0.143
Cardiac failure, *n* (%)	3 (5.7)	0	3 (9.4)	0.269
Other events, *n* (%)	5 (9.4)	0	5 (15.6)	0.144
AEs (grade 3)	4	1	3	
Anemia, *n* (%)	2 (3.8)	1 (4.8)	1 (3.1)	> 0.999
Cardiac failure, *n* (%)	2 (3.8)	0	2 (6.3)	0.512
THEs, *n* (%)	12 (22.6)	3 (14.3)	9 (28.1)	0.323
Thrombotic events, *n* (%)	8 (15.1)	1 (4.8)	7 (21.9)	0.126
Hemorrhagic events, *n* (%)	4 (7.5)	2 (9.5)	2 (6.3)	> 0.999
Transformation, *n* (%)	3 (5.7)	1 (4.8)	2 (6.3)	> 0.999
MF, *n* (%)	3 (5.7)	1 (4.8)	2 (6.3)	> 0.999

AE adverse event, *THEs* thrombohemorrhagic events, *MF* myelofibrosis

of anagrelide was 1.0 mg/day or higher. However, no other studies have focused on the efficacy and safety of anagrelide initiated at lower doses in a group of first-onset ET patients. Although this study was conducted in a small number of patients, it is the first retrospective comparison of the effects and safety of anagrelide according solely to its starting dose.

The therapeutic effects and observed adverse events/THEs in all patients were similar to those observed in previous reports [13, 15, 17, 24–34, 36–39]. Regarding the therapeutic effects, the previously reported CR rates were approximately 50–70%, and the response rates, including PR rates, was approximately 90% [40], which is consistent with the rate of 84.9% (CR + PR) reported in this study. Regarding adverse events, the previously reported overall incidence rates were 20.2–100%, consisting mainly of headache (5.1–58.3%), palpitations (4.0–70%), diarrhea (1.0–35.8%), and cardiovascular adverse events (27–46.7%) caused by the inhibitory action of anagrelide on phosphodiesterase III activity. However, most of these adverse events become mild to moderate following continuous administration, and they are subsequently alleviated/resolved. Although the overall discontinuation rates of anagrelide were 7–50% [13, 15, 17, 24–34, 36, 38, 39], the median rate of discontinuation due to adverse events was approximately 10%, similar to the rate observed in the present study (9.4%). Concerning the incidence of THEs, although the definition of THEs differs among reports such as the Primary Thrombocythaemia 1 (PT-1) trial [32] and the ANAHYDRET study [36], our findings were roughly comparable to those reported previously [27, 32, 36].

In this study, it is noteworthy that, compared with the findings in patients who started anagrelide at 1.0 mg/day (group B), the patients who started anagrelide at 0.5 mg/day (group A) had a lower median daily dose of anagrelide, lower incidences of all adverse events and palpitations (a major adverse event), a lower percentage of patients who switched to hydroxyurea, and a lower anagrelide discontinuation rate, all while maintaining good control of the platelet count. Only a few clinical studies have evaluated a switching dose of 0.5 mg/day anagrelide in patients who were intolerant or poorly responsive to cytoreductive therapies [33, 38]. Although one of these studies did not divide its subjects according to the starting dose of anagrelide (0.5 or 1.0 mg/day), patients were divided between those who discontinued previous cytoreductive therapy before anagrelide treatment at 1.0 mg/day (median) and those who discontinued previous therapy after the initiation of anagrelide at 0.5 mg/day (median) [38]. The continuation rate of anagrelide was favorable in the subgroup with a starting dose of 0.5 mg/day. Another study started anagrelide therapy in 52 patients at 0.5 mg/day, 36 of whom had ET patients and approximately half had a prior history of cytoreductive therapy [29], and the mean maintenance dose was slightly lower (1.7 mg/day) than previously reported, whereas the incidence rates of headache and palpitations were comparable to those reported previously [13, 15, 17, 24–28, 30–34, 36–39]. According to a report indicating that cardiovascular adverse events had a significant relationship with a higher anagrelide induction dose but a low impact on the discontinuation of anagrelide [34], the factor contributing to the development of cardiovascular adverse events might be the starting dose of anagrelide. Considering the incidence of adverse events and discontinuation rates of anagrelide in previous studies that used high starting doses, the anagrelide-related adverse events were considered dose dependent. As demonstrated in this study, initiating anagrelide at a lower dose can reduce the frequency of adverse events during the early phase of treatment and the rate of anagrelide discontinuation, as well as permit careful dose escalation at an appropriate timing while monitoring for the onset of adverse events. As a result, the platelet count may be well controlled with a low maintenance dose.

Because all six patients with heart failure displayed high platelet counts before starting anagrelide administration in our study, treatment was initiated at 1.0 mg/day, and cardiac adverse events were observed frequently (five out of the six patients). Therefore, in patients with heart failure, it may be reasonable to start anagrelide at a lower dose, followed by a gradual dose increase with regular monitoring.

One of the limitations of this study was that the platelet count before the initiation of anagrelide treatment tended to be higher in group B, which may have led to selection bias because the attending physicians started anagrelide at 1.0 mg/day. This was also the case for all six patients with heart failure. In addition, the rate of adverse events may have been underestimated because this was a retrospective study based on the patient medical records maintained by their attending physicians. Most important factor for this analysis is how and when the doctor increases the dose of anagrelide in clinical practice. However, these factors are difficult to compare and analyze in this study.

In conclusion, the recommended starting dose for anagrelide in the package insert is 1.0 mg/day or higher, but responsiveness to treatment and the appropriate starting and maintenance doses may differ between individual patients. If conditions permit, starting at a dose of 0.5 mg/day followed by careful and steady dose escalation may result in fewer adverse events, a lower discontinuation rate, and a lower maintenance dose. Initiating anagrelide at a lower dose may be considered a useful approach in the real-world setting.

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Compliance with ethical standards

Conflict of interest Tomoki Ito reports receiving honoraria from Takeda Pharmaceutical Co., Ltd. Yoshinori Hashimoto reports receiving honoraria from Shire Japan K.K. The other authors declare that they have no conflict of interest.

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