Safety and efficacy of anagrelide in Japanese post-marketing surveillance, with subgroup analyses on the effect of previous cytoreductive therapies, age, and starting dose

Norio Komatsu1,2,3 · Yoshinori Hashimoto1,2,3,4 · Terumi Baba5 · Manami Otsuka5 · Takafumi Akimoto5 · Jovelle Fernandez5

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Abstract

Background In Japan, anagrelide has been approved for use in patients with essential thrombocythemia. Here, the safety and efficacy of anagrelide was assessed in clinical practice as post-marketing surveillance. Subgroup analyses were conducted to compare patients (1) with or without a history of cytoreductive therapy (CRT), (2) <60 or ≥60 years of age, and (3) with an anagrelide starting dose of ≤0.5 mg/day or 1.0 mg/day.

Methods Data were collected for all patients who received anagrelide, with an observation period of 12 months after treatment initiation.

Results Of the 648 patients, 54.3% experienced adverse drug reactions (ADRs). The most commonly reported ADRs were headaches, palpitations, and anemia. No significant difference was observed in overall ADRs across patient subgroups. A significantly higher incidence of headaches was observed in patients < 60 years versus those ≥ 60 years (P < 0.001). The incidence of anemia and serious ADRs were significantly higher in patients ≥ 60 years, and those with a history of CRT (P < 0.05). The discontinuation rate at 6 months was significantly lower in patients started at the lower anagrelide dose (P < 0.05). Platelet counts decreased in all analyzed groups.

Conclusions This surveillance showed that anagrelide has a tolerable safety and efficacy profile.

Keywords Anagrelide · Essential thrombocythemia · Japanese · Post-marketing surveillance

Introduction

Essential thrombocythemia (ET) is a myeloproliferative neoplasm resulting from driver gene mutations in JAK2, CALR, and MPL in hematopoietic stem cells. It is characterized by increased production of megakaryocytes and platelets [1]. ET is associated with an increased risk of thrombosis and/or hemorrhage as well as progression to myelofibrosis or leukemia which are in turn associated with increased mortality and morbidity [2, 3]. One of the main treatment goals for ET is to reduce the platelet count to prevent the onset of thrombohemorrhagic events [4, 5].

In patients who have a high-risk of developing thrombosis, cytoreductive therapy (CRT) and antiplatelet therapy have been endorsed within some guidelines [6–8]. Anagrelide is a cytoreductive agent, and although its mechanism of platelet reduction is not well understood, it has been theorized to selectively suppress the mRNA expression of GATA-1 and FOG-1 transcription factors. This results in the
inhibition of megakaryocyte differentiation from hematopoietic stem cells [9]. In addition, anagrelide also suppresses proplatelet formation, thereby reducing platelet counts [10].

A Phase III study in high-risk Japanese patients with ET showed that anagrelide reduced platelet counts with a safety profile consistent with the findings that supported the approval of anagrelide in Europe and the United States [11]. As a result of these findings, anagrelide was granted approval in September 2014 for the treatment of ET in Japan [11, 12]. Only a limited number of patients (N=53) were enrolled in the Phase III Japanese study, which focused on high-risk patients with ET who were refractory or intolerant to hydroxycarbamide [11]. Anagrelide has also been approved for treatment-naïve patients with ET based on the results of two global clinical studies; ANAHYDRET and a Phase IIIb clinical study for anagrelide [13, 14]. Therefore, the safety and efficacy findings for anagrelide in CRT-naïve Japanese patients are limited [15, 16].

Interestingly, there has been less concern regarding secondary malignancy developing in patients taking anagrelide than some alternative therapies, and it has been indicated that a higher proportion of younger patients receive anagrelide [17]. To date, limited data have been presented comparing the safety and efficacy of anagrelide between patients who are <60 years of age and those who are ≥60 years of age. Furthermore, the starting dose of anagrelide, as per the prescribing information, is 1.0 mg/day; however, in the previous Japanese study, the rate of adverse drug reactions (ADRs) was significantly lower in patients taking a lower starting dose of 0.5 mg/day [16].

The aim of this multicenter, post-marketing surveillance was to investigate the safety and efficacy of anagrelide treatment under daily clinical conditions after its approval and introduction in Japan. This surveillance also compared the safety and efficacy of anagrelide in patients: 1) with and without a history of CRT, 2) <60 and ≥60 years of age, and 3) taking different starting doses of anagrelide (≤0.5 and 1.0 mg/day).

The observational period was 12 months, starting from the day of treatment initiation with anagrelide. Case report forms (CRFs) were collected in two batches during the observational period; CRF Volume 1 was collected from treatment initiation to 6 months and CRF Volume 2 was collected from months 7–12. For the patients who discontinued anagrelide, the data were collected up to the time of discontinuation.

**Patients**

Patients who had started treatment with anagrelide between 25 November 2014 and 31 May 2015 in Japan were included in this surveillance. The patient disposition is shown in Supplementary Fig. 4. Patients who had received at least 1 dose of anagrelide after enrollment and had safety data, were included in the safety analysis set. Of the patients in the safety analysis set, those who had their platelet count measured at enrollment and at least once after the start of anagrelide treatment were included in the efficacy analysis set. Because the objective of this surveillance was to investigate the safety and efficacy of anagrelide under daily clinical conditions, ET diagnosis was performed at the physicians’ discretion. Gene mutation analysis and bone marrow biopsies were not mandatory.

The safety and efficacy of anagrelide was compared in patients categorized into the following subgroups: (1) with and without a history of CRT, (2) <60 and ≥60 years of age, and (3) taking different starting doses of anagrelide (≤0.5 and 1.0 mg/day). Patients who had received anagrelide before registration of this surveillance were excluded from the subgroup analyses due to the patients’ characteristics at the start of this surveillance being different from those at the time they started treatment with anagrelide.

**Assessments**

Treatment-emergent adverse events (TEAEs) considered to be related to anagrelide were defined as ADRs. The ADRs were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 22.0. Patients with multiple events of the same pre-defined event category were only recorded once.

The primary efficacy outcome of the surveillance was to evaluate the proportion of patients who had a response in platelet count (<600×10^9/L) beyond 3 months (≥91 days) after the start of treatment with anagrelide. The secondary efficacy outcomes were to evaluate the proportion of patients who: (a) had a platelet response rate <400×10^9/L beyond 3 months (≥91 days) after the start of administration, and
(b) achieved a 50% reduction in platelet count at any time after anagrelide administration versus their baseline values.

**Statistical analysis**

Patient characteristics, incidence of ADRs, rate of discontinuation, and platelet reduction and control rate were analyzed with the Chi-square or Fisher’s exact test to determine statistical significance. Univariable and multivariable analyses using logistic regression were conducted to identify risk factors for anemia. For these tests, the two-sided significance level of 95% was selected. Factors were considered to be statistically significant when the *P* value was < 0.05. Statistical analyses were performed using Statistical Analysis Software (SAS) Version 9.4 (or higher) within a controlled environment.

**Results**

**Patient disposition, baseline demographics, and disease characteristics**

Overall, 689 patients were registered in this surveillance (Supplementary Fig. 4). The first group of CRF (Volume 1; data from treatment initiation to 6 months) was collected from 679 patients, and CRF Volume 2 (data from months 7–12) was collected from 458 patients. A total of 648 patients received 1 or more doses of anagrelide and had one or more post-baseline safety assessment (the Safety Analysis set). The Efficacy Analysis set comprised 478 patients who had a history of CRT (not-CRT naïve). Patient characteristics according to their history of CRT are shown in Supplementary Table 6. The patients in Group A comprised 146 patients who had no history of CRT (CRT naïve), and Group B comprised 478 patients who had a history of CRT (not-CRT naïve). Patient characteristics according to their history of CRT are shown in Supplementary Table 6. The patients in Group B were significantly older and were more likely to have had a history of thrombohemorrhagic events compared with Group A (*P* < 0.001 and *P* < 0.05, respectively). As a result, there were significantly more high-risk patients in Group B than in Group A (*P* < 0.001).

**Safety and efficacy according to patients’ history of CRT**

A subgroup analysis was conducted according to the patients’ history of CRT. Group A comprised 146 patients who had no history of CRT (CRT naïve), and Group B comprised 478 patients who had a history of CRT (not-CRT naïve). Patient characteristics according to their history of CRT are shown in Supplementary Table 6. The patients in Group B were significantly older and were more likely to have had a history of thrombohemorrhagic events compared with Group A (*P* < 0.001 and *P* < 0.05, respectively). As a result, there were significantly more high-risk patients in Group B than in Group A (*P* < 0.001).

The incidence of all ADRs was 49.3% (72 patients) in Group A and 56.7% (271 patients) in Group B (Table 1). Although the rate of ADRs was slightly lower in Group A than in Group B, the difference was not significant (*P* = 0.129). Notably, the incidence of anemia was significantly higher in Group B than in Group A (reported in 37 [7.7%] and 4 patients [2.7%], respectively; *P* < 0.05). Of the serious ADRs, 3.4% (5 patients) were reported in Group A and 9.6% (46 patients) were reported in Group B (*P* < 0.05). The most frequently reported serious ADR across both groups was cardiac failure (1.0%; 6 patients); however, this ADR was observed only in Group B.

The proportion of patients whose platelet count had decreased by 50% or more from baseline was 53.9% in Group A, and this was significantly higher than that of...
reported for Group B ($P < 0.001$, Fig. 1). Conversely, there were no significant differences in the proportion of patients whose platelet count had decreased below $600 \times 10^9/L$ or $400 \times 10^9/L$ beyond 3 months ($\geq 91$ days) after baseline between Group A and Group B ($P = 0.373$, and $P = 0.585$, respectively).

**Safety and efficacy according to patients’ age**

The safety and efficacy findings were compared between patients < 60 years of age (Group C), and patients ≥ 60 years of age (Group D). One patient was excluded, because their age was unknown. The number of patients with a history of CRT was significantly higher in Group D than in Group C, and platelet count was significantly lower in Group D than in Group C ($P < 0.001$ and $P < 0.05$, respectively, Supplementary Table 7). Furthermore, there were more patients with a history of complications, including cardiac disorders in Group D than in Group C ($P < 0.001$).

The incidence of all ADRs was 53.9% (97/180 patients) in Group C and 55.5% (246/443 patients) in Group D, and there was no significant difference between the groups ($P = 0.723$, Table 2). Interestingly, headache was reported for 27.8% (50 patients) of Group C, and this incidence was significantly higher than that reported for Group D (11.1%, 49 patients; $P < 0.001$). In contrast, anemia was reported for 8.1% (36 patients) in Group D and 2.8% in Group C (5 patients; $P < 0.05$). Similarly, the majority of patients who experienced serious ADRs were in Group D ($P < 0.001$).

In the efficacy analysis, the primary outcome (platelet count < $600 \times 10^9/L$ beyond 3 months [$\geq 91$ days] after baseline) was achieved for a significantly higher proportion of Group D than of Group C ($P < 0.001$). No significant differences were observed for the secondary outcomes, including the proportion of patients with a platelet response rate of $< 400 \times 10^9/L$ beyond 3 months ($\geq 91$ days) after baseline and the proportion of patients who achieved a
50% reduction in platelet count versus their baseline values ($P = 0.128$, and $P = 0.786$, respectively, Fig. 2).

### Safety and efficacy according to the starting dose of anagrelide

The number of patients who started on $\leq 0.5$ mg/day of anagrelide was 135 (Group E), and 475 patients started on 1.0 mg/day (Group F). The prescribing information specifies that the starting dose of anagrelide is 1.0 mg/day, and consequently, the 14 patients who started with a dose of more than 1.0 mg/day were excluded from this analysis. Although more patients in Group F had cardiac disorders, there were no significant differences between the patient characteristics when comparing Groups E and F (Supplementary Table 8). The incidence of all ADRs was reported for 48.9% (66 patients) of patients in Group E and 56.6% (269 patients) of patients in Group F, respectively (Table 3). There was no significant difference between these groups ($P = 0.118$). Similarly, there was no significant difference between groups when assessing the rates of all serious ADRs ($P = 0.859$). The main serious ADRs were cardiac disorders (such as cardiac failure or atrial fibrillation), most of which occurred in Group F. Furthermore, the discontinuation rate of anagrelide within the first 6 months of treatment was significantly lower in Group E than in Group F ($P < 0.05$, Supplementary Table 9). Among the many reasons for discontinuation, the most common cause was adverse events.

Although the efficacy findings for Group F (66.4% [213/321 patients]) appeared to be more favorable than those of Group E (57.0% [57/100 patients]), there was no significant difference in the primary outcome of the efficacy analysis (platelet count $< 600 \times 10^9$/L beyond 3 months [$\geq 91$ days] after baseline; $P = 0.096$, Fig. 3).

**Table 2** Incidence of ADRs according to patients’ age as per MedDRA, version 22.0. terms

| ADRs, n (%) | Total (N=623) | Group C <60 years (n=180) | Group D $\geq$60 years (n=443) | Group C vs Group D $P$ value |
|------------|---------------|---------------------------|--------------------------------|-----------------------------|
| All ADRs   | 343 (55.1)    | 97 (53.9)                 | 246 (55.5)                     | 0.723                       |
| Headache   | 99 (15.9)     | 50 (27.8)                 | 49 (11.1)                      | <0.001                      |
| Palpitations| 90 (14.4)     | 31 (17.2)                 | 59 (13.3)                      | 0.211                       |
| Anemia     | 41 (6.6)      | 5 (2.8)                   | 36 (8.1)                       | <0.05                       |
| Diarrhea   | 37 (5.9)      | 8 (4.4)                   | 29 (6.5)                       | 0.356                       |
| Peripheral edema | 23 (3.7) | 6 (3.3) | 17 (3.8) | 1.000                       |
| Other      | 231 (37.1)    | 57 (31.7)                 | 174 (39.3)                     | 0.082                       |
| All serious ADRs | 51 (8.2) | 3 (1.7) | 48 (10.8) | <0.001                      |
| Cardiac failure | 6 (1.0) | 1 (0.6) | 5 (1.1) | 0.678                       |
| Atrial fibrillation | 3 (0.5) | 0 (0.0) | 3 (0.7) | NA                          |
| Cerebral infarction | 3 (0.5) | 0 (0.0) | 3 (0.7) | NA                          |
| Electrocardiogram QT prolonged | 3 (0.5) | 0 (0.0) | 3 (0.7) | NA                          |
| Renal impairment | 3 (0.5) | 0 (0.0) | 3 (0.7) | NA                          |
| Other      | 36 (5.8)      | 2 (1.1)                   | 34 (7.7)                       | <0.001                      |

ADR adverse drug reactions, NA not applicable

Fig. 2 Platelet reduction and control rate for patients in the efficacy analysis set, comparing those who were $< 60$ years of age (Group C) and those who were $\geq 60$ years of age (Group D). $^a$Platelet count had decreased below $600 \times 10^9$/L beyond 3 months ($\geq 91$ days) after baseline. $^b$Platelet count had decreased below $400 \times 10^9$/L beyond 3 months ($\geq 91$ days) after baseline. $^c$Platelet count had decreased by 50% or more at any time after anagrelide administration from that at baseline.
In this surveillance, subgroup analyses findings may assist with the management of anagrelide treatment in certain groups of patients. To the best of our knowledge, this is the first evaluation of patients treated with anagrelide comparing those: (1) with or without a history of CRT; and (2) < 60 and ≥ 60 years of age.

The most frequently reported ADR in the Phase III study investigating anagrelide in Japanese patients was anemia (47.2%, 25/53 patients) [11]. Anemia in both this surveillance and the Phase III study may be due to the myelosuppression resulting from a history of CRT. In this surveillance, the incidence of anemia was significantly higher in Group B, patients who had a history of CRT, and Group D, patients ≥ 60 years of age (Tables 1, 2). However, analyses to identify risk factors for anemia suggested that age ≥ 60 years and history of CRT may have been confounding factors (Supplementary Table 10). Although history of CRT was not an independent risk factor for anemia in the present analysis, patients with history of CRT should be closely monitored for worsening anemia when treated with anagrelide, partly because of myelosuppression caused by previous CRT. Additionally, the incidence of anemia was 6.6% (43/648 patients) in the overall patient population, and this was similar to the rates reported in the UK-PT1 study (7.9%) and the ANAHYDRET study (9.0%) [13, 18]. These results suggest that the incidence of anemia is similar between Japanese and non-Japanese patients; however, hemoglobin levels should still be monitored under daily clinical conditions, especially for patients with a history of CRT, and those who are ≥ 60 years of age.

The most frequent serious ADRs were related to cardiac disorders, which occurred in Group B (history of CRT), Group D (≥ 60 years of age), and Group F (1.0 mg/day starting dose; Tables 1, 2, 3). The patients in these groups either had a history of, or experienced complications of cardiac disorders, which included cardiac failure, atrial fibrillation, cerebral infarction, electrocardiogram QT prolonged, renal impairment, and other serious ADRs (Supplementary Table 10). These results suggest the need for close monitoring of patients with a history of CRT, especially those who are ≥ 60 years of age.

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### Discussion

In this surveillance, subgroup analyses findings may assist with the management of anagrelide treatment in certain groups of patients. To the best of our knowledge, this is the first evaluation of patients treated with anagrelide...
disorders at baseline (Supplementary Tables 6, 7, and 8). Of all 9 patients with serious ADRs of cardiac failure \( (n = 6) \) or atrial fibrillation \( (n = 3) \), 5 patients had a history of cardiac complications. A previous study investigating anagrelide use in 55 patients showed that it was difficult to predict cardiac adverse events, even if in-depth cardiovascular monitoring was performed [19]. Another study showed that the starting dose of anagrelide was significantly higher in patients who experienced cardiovascular adverse events compared with the patients who did not experience any cardiovascular events [20]. These findings indicate that cardiovascular monitoring should be regularly conducted in daily clinical practice to identify and manage any cardiac adverse events in patients taking anagrelide. This is particularly relevant for patients who have a history or have had complications of cardiac disorders prior to the start of treatment. In addition, it may be beneficial to start patients on a lower dose of anagrelide, and then gradually increase the dose while monitoring for any cardiac adverse events [16].

Anagrelide is able to inhibit phosphodiesterase III activity, leading to peripheral vasodilation, which can cause headaches [21]. The cause of patients < 60 years of age having more headaches than those ≥ 60 years of age within this surveillance is unknown. It is worth noting that because headaches are reported to be a symptom of ET, it cannot be ruled out that the headaches that physicians reported as ADRs following treatment with anagrelide could instead have been caused by ET. The median dose of anagrelide was 1.50 mg (range 0.50–7.44 mg) in patients < 60 years of age versus 1.44 mg (range 0.25–5.13 mg) in patients ≥ 60 years of age, and no significant difference was observed \( (P = 0.994) \). One possible reason for younger patients experiencing more headaches is that their blood vessels have more elasticity and so are more flexible. It is recommended that more attention should be paid to headaches in younger patients who are taking anagrelide and pain relief (e.g., acetaminophen) may be prescribed to assist with this if needed.

As per the efficacy analysis findings, the median daily dose of anagrelide was 1.29 mg (range 0.25–3.57 mg) in Group E \( ( \leq 0.5 \text{ mg/day starting dose}) \) and 1.47 mg (range 0.31–7.44 mg) in Group F \( (1.0 \text{ mg/day starting dose}) \), and the difference between the groups was significant \( (P < 0.001) \). The findings within this surveillance agree with those of a previous study investigating anagrelide starting doses, which found that the lower starting dose of 0.5 mg/day resulted in fewer discontinuations [16]. Interestingly, in terms of the primary outcome, Group F showed more improvement than Group E, and although this difference was not significant and no differences were noted between the two groups for the secondary efficacy outcomes, this result suggests that a lower starting dose should not affect treatment efficacy (Fig. 3). Taken together, these findings suggest that starting patients on a lower dose of anagrelide may reduce the risk of developing adverse events, and in turn, avoid treatment discontinuation due to adverse events.

In the subgroup analysis, significant differences were observed for the secondary outcome (control rate of 50% or more); however, this was not observed in the primary outcome between Group A; CRT-naïve patients and Group B; not-CRT naïve (Fig. 1). The reason for this is likely that Group A patients started anagrelide treatment with a higher platelet count and many patients may therefore have had a platelet count that decreased below 50% or more, but not below \( < 600 \times 10^9/L \). Alternatively, these patients were not targeted below \( < 600 \times 10^9/L \), because Group A had a higher proportion of low-risk patients (Supplementary Table 6).

The primary efficacy outcome according to age subgroups was significantly higher in Group D \( (\geq 60 \text{ years of age}) \) than in Group C \( (< 60 \text{ years of age}) \) [Fig. 2]. The patient demographic data for the safety analysis set indicated that almost all patients in Group C were low risk \( (95.0\%) \); however, 113 patients \( (62.8\%) \) had a history of CRT (Supplementary Table 7). Nevertheless, the platelet count had been significantly higher at baseline in the patients of Group C than those of Group D \( (P < 0.05, \text{ Supplementary Table 7}) \), which may explain the above result. Interestingly, there were more JAK2V617F negative patients in Group C \( (33.9\%, 61 \text{ patients}) \) compared with Group D \( (18.1\%, 80 \text{ patients}) \). Overall, there were no significant differences observed across each secondary outcome (Fig. 2), and taken together, these findings indicate that the efficacy of anagrelide should be favorable even for patients without the JAK2V617F mutation.

This surveillance has several limitations. Gene mutation analysis and bone marrow biopsies were not performed for some patients. As a result, the patients who could have polycythemia vera or prefibrotic myelofibrosis according to the World Health Organization 2016 criteria, may be included in this analysis [22]. In this surveillance, ADRs were reported at the attending physicians’ discretion, and as a result, may be underestimated. Serious hemorrhage was reported in 6 patients \( (0.93\%) \), and all cases recovered. Of these, 5 patients were receiving concomitant aspirin treatment. Although anagrelide treatment may raise concerns regarding hemorrhagic risk in combination with antiplatelet therapy (e.g., aspirin), or disease transformation (e.g., myelofibrosis), these conditions were not further investigated in this surveillance. Future studies will need to address these issues in more detail.

In conclusion, the safety and efficacy of anagrelide are supported by the findings in this surveillance, which found that patients taking anagrelide ≥ 60 years of age and those with a history of CRT are monitored for signs of anemia and other serious ADRs. Care should also be taken regarding headaches in
patients < 60 years of age. Starting patients on a lower dose of anagrelide therapy may reduce the risk of adverse events and also avoid treatment discontinuation.

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**Availability of data and materials** The datasets, including the redacted surveillance protocol, redacted statistical analysis plan, and individual participants’ data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymization.

**Declarations**

**Conflict of interest** NK is a board member of PharmaEssentia Japan. NK received personal fees from Novartis, PharmaEssentia, AbbVie, Celgene, Japan Tobacco International, and Otsuka, and grants from Takeda/Shire, Novartis, FUJIFILM Wako Pure Chemical Corporation, Fuso Pharmaceutical Co. Ltd, Pfizer, Perseus Proteomics, Otsuka, Chugai, Kyowa Kirin, Sumitomo Dainippon Pharma, and Bristol-Myers Squibb. NK and YH received personal fees from Takeda/Shire. NK and YH received personal fees from Novartis, PharmaEssentia, AbbVie, Celgene, Japan Tobacco International, and Otsuka, and grants from Takeda/Shire, Novartis, FUJIFILM Wako Pure Chemical Corporation, Fuso Pharmaceutical Co. Ltd, Pfizer, Perseus Proteomics, Otsuka, Chugai, Kyowa Kirin, Sumitomo Dainippon Pharma, and Bristol-Myers Squibb. NK and YH received personal fees from Meiji Seika Pharma and PharmaEssentia Japan. TB is an employee of Takeda/Shire and is a student in the Department of Hematology, Juntendo University Graduate School of Medicine. MO and TA are employees of Takeda/Shire. JF is an employee of Takeda and owns restricted stocks in GSK and Takeda.

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**References**

1. Vainchenker W, Kralovics R. Genetic basis and molecular pathophysiology of classical myeloproliferative neoplasms. Blood. 2017;129(6):667–79.
2. Cortelazzo S, Viero P, Finazzi G, D’Emilio A, Rodeghiero F, Barbui T. Incidence and risk factors for thrombotic complications in a historical cohort of 100 patients with essential thrombocythemia. J Clin Oncol. 1990;8(3):556–62.
3. Tefferi A, Guglielmelli P, Larson DR, Finke C, Wassei EA, Pieri L, et al. Long-term survival and blast transformation in molecularly annotated essential thrombocythemia, polycythemia vera, and myelofibrosis. Blood. 2014;124(16):2507–13.
4. Briere JB. Essential thrombocythemia. Orphanet J Rare Dis. 2007;2:3.
5. Tefferi A, Barbui T. Polycythemia vera and essential thrombocythemia: 2021 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(12):1599–613.
6. Barbui T, Tefferi A, Vannucchi AM, Passamonti F, Silver RT, Hoffman R, et al. Philadelphia chromosome-negative classical myeloproliferative neoplasms: revised management recommendations from European LeukemiaNet. Leukemia. 2018;32(5):1057–69.
7. Mesa RA, Jamieson C, Bhatia R, Deininger MW, Fletcher CD, Gerds AT, et al. NCCN guidelines insights: myeloproliferative neoplasms, version 2.2018. J Natl Compr Canc Netw. 2017;15(10):1193–207.
8. Shimoda K, Takahashi N, Kiriito K, Iriyama N, Kagawuchi T, Kizaki M. JSH practical guidelines for hematological malignancies, 2018: I. Leukemia-4. Chronic myeloid leukemia (CML)/myeloproliferative neoplasms (MPN). Int J Hematol. 2020;112(3):268–91.
9. Ahluwalia M, Donovan H, Singh N, Butcher L, Erusalimsky JD. Anagrelide represses GATA-1 and FOG-1 expression without interfering with thrombopoietin receptor signal transduction. J Thromb Haemost. 2010;8(10):2252–61.
10. Espasandin YR, Glembotsky AC, Grodzierski M, Lev PR, Goette NP, Molinas FC, et al. Anagrelide platelet-lowering effect is due to inhibition of both megakaryocyte maturation and proplatelet formation: insight into potential mechanisms. J Thromb Haemost. 2015;13(4):631–42.
11. Kanakura Y, Miyakawa Y, Wilde P, Smith J, Achenbach H, Okamoto S. Phase III, single-arm study investigating the efficacy, safety, and tolerability of anagrelide as a second-line treatment in high-risk Japanese patients with essential thrombocythemia. Int J Hematol. 2014;100(4):533–60.
12. Kanakura Y, Shirasugi Y, Yamaguchi H, Koike M, Chou T, Okamoto S, et al. A phase 3b, multicenter, open-label extension study of the long-term safety of anagrelide in Japanese adults with essential thrombocythemia. Int J Hematol. 2018;108(5):491–8.
13. Gisslinger H, Gotic M, Holowiecki J, Penka M, Thiele J, Kvasnicka HM, et al. Anagrelide compared with hydroxyurea in WHO-classified essential thrombocythemia: the ANAHYDRET study, a randomized controlled trial. Blood. 2013;121(10):1720–8.
14. Gotic M, Egyed M, Gercheva L, Warzocha K, Kvasnicka HM, Achenbach H, et al. Cardiovascular safety of anagrelide hydrochloride versus hydroxyurea in essential thrombocythemia. Cardiovasc Toxicol. 2021;21(3):236–47.
15. Ito T, Hashimoto Y, Tanaka Y, Nakaya A, Fujita S, Satake A, et al. Efficacy and safety of anagrelide as a first-line drug in cytoreductive treatment-naïve essential thrombocythemia patients in a real-world setting. Eur J Haematol. 2019;103(2):116–23.
16. Hashimoto Y, Ito T, Tanaka Y, Nakaya A, Fujita S, Satake A, et al. 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. Int J Hematol. 2020;112(1):33–40.

17. Birgegard G, Besses C, Grieshammer M, Gugliotta L, Harrison CN, Hamdani M, et al. Treatment of essential thrombocythemia in Europe: a prospective long-term observational study of 3649 high-risk patients in the Evaluation of Anagrelide Efficacy and Long-term Safety study. Haematologica. 2018;103(1):51–60.

18. Harrison CN, Campbell PJ, Buck G, Wheatley K, East CL, Barford D, et al. Hydroxyurea compared with anagrelide in high-risk essential thrombocythemia. N Engl J Med. 2005;353(1):33–45.

19. Tortorella G, Piccin A, Tieghi A, Marcheselli L, Steurer M, Gastl G, et al. Anagrelide treatment and cardiovascular monitoring in essential thrombocythemia. A prospective observational study. Leuk Res. 2015;39(6):592–8.

20. Gugliotta L, Tieghi A, Tortorella G, Scalzulli PR, Ciancia R, Lunghi M, et al. Low impact of cardiovascular adverse events on anagrelide treatment discontinuation in a cohort of 232 patients with essential thrombocythemia. Leuk Res. 2011;35(12):1557–63.

21. Frewin R, Dowson A. Headache in essential thrombocythaemia. Int J Clin Pract. 2012;66(10):976–83.

22. Arber DA, Orazi A, Hasserjian R, Thiele J, Borowitz MJ, Le Beau MM, et al. The 2016 revision to the World Health Organization classification of myeloid neoplasms and acute leukemia. Blood. 2016;127(20):2391–405.

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