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Anagrelide for platelet-directed cytoreduction in polycythemia vera: Insights into utility and safety outcomes from a large multi-center database

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Abstract

Anagrelide (ANA) is a platelet-specific cytoreductive agent utilized in the guideline-directed management of high-risk essential thrombocythemia. In the context of polycythemia vera (PV), ANA is occasionally employed in clinical practice, although data has not consistently demonstrated a benefit to targeting a platelet goal as a therapeutic endpoint. The aim of the current

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.leukres.2022.106903.

study was to delineate the patterns of ANA use in PV, and to describe outcomes and toxicities. Within a multi-center cohort of 527 patients with PV, 48 received ANA (9 excluded for absent data). 27 (69.2%) had high-risk PV, 10 (25.6%) had prior thrombosis, and none had extreme thrombocytosis, acquired von Willebrand disease, and/or documented resistance to hydroxyurea. While ANA effectively lowered median platelet count, 43.5% of patients had an unresolved thrombocytosis at time of ANA discontinuation. Treatment-emergent adverse events—including headaches, cardiac palpitations and arrhythmias, nausea, vomiting and/or diarrhea—led to ANA discontinuation in 76.9% of patients. Further, three patients experienced arterial thromboses during a median duration of 27.5 months of ANA therapy. In conclusion, this study highlights ANA's restrictive tolerability profile which, compounded by the absence of clear advantage to strict platelet control in PV, suggests the use of ANA should be limited in this setting.

Keywords

Anagrelide; Polycythemia vera; Thrombocytosis

1. Introduction

Polycythemia vera (PV) is one of the *BCR-ABL1*-negative chronic myeloproliferative neoplasms (MPNs), uniquely characterized by the presence of absolute erythrocytosis, often with concomitant leukocytosis and thrombocytosis. Patients with PV are at an increased risk for thrombohemorrhagic events, as well as disease progression to secondary myelofibrosis (MF) and transformation to acute myeloid leukemia (AML). The therapeutic landscape for PV is evolving; agents with potential disease-modifying activity such as interferon-α (IFN-α) have recently been Food and Drug Administration (FDA)-approved, and others such as the MDM2 inhibitor idasanutlin are in clinical testing [1–3]. However, to date no treatment has definitively demonstrated evidence of cure [4]. As such, the immediate goals of available therapy remain thrombohemorrhagic risk reduction and alleviation of symptom burden [5].

Management of patients with PV is guided by a risk-adapted approach, wherein those patients younger than 60 years and without a history of prior arterial or venous thrombosis are classified as having low-risk disease, and their treatment comprised of low-dose aspirin, therapeutic phlebotomy, and aggressive management of cardiovascular risk factors [6–8]. Cytoreductive therapy with agents such as hydroxyurea (HU), pegylated IFN-α, and/or busulfan is typically reserved for those falling within the high-risk category [5,9–11], and targeted therapy with the *JAK*1/2 inhibitor ruxolitinib is appropriate in those with refractory symptoms, treatment intolerance, or an inadequate therapeutic response [9,12,13].

The clinical benefit of targeted cytoreduction of thrombocytosis associated with PV, however, is not clearly established in the literature. While European LeukemiaNet (ELN) criteria for a complete response (CR) require a platelet count of less than 400×10^9/L, this laboratory goal has not been validated [14,15]. A *post-hoc* analysis of the ECLAP study found elevated platelet counts to be associated with reduced rates of disease progression, whilst having no significant relationship with thrombotic risk or mortality

[16]. A multivariable analysis of patients with WHO-defined PV (n = 1545) within a large multi-center study found thrombocytosis to be favorable in terms of overall survival (HR 0.70, 95% C.I. 0.60–0.98; p = 0.03) [17]. Some studies have previously suggested an association between thrombocytosis and bleeding diathesis in patients with PV, but the data has been inconsistent and may be reflective of a higher hemorrhagic risk associated with extreme thrombocytosis due to resultant acquired von Willebrand disease (aVWD) [6, 16]. Accordingly, the most recent PV management guidelines from the National Comprehensive Cancer Network (NCCN) and ELN only suggest initiation of cytoreductive therapy for thrombocytosis if symptomatic, or if platelet count is greater than 1500×10^9/L, respectively [5,9]. More recently, an analysis of the REVEAL study evaluating 2271 patients with PV suggested an association between a post-enrollment platelet count of $> 400 \times 10^9$/L as a binary time-dependent covariate and increased thromboembolic risk (HR 1.60, 95% C.I. 1.088–2.359; p = 0.017), although interpretation of this outcome would be augmented by inclusion of additional covariate-adjusted analyses that would account for the use of aspirin and distinguish between the use of other specific concomitant therapies [18].

Anagrelide (ANA) is an imidazoquinoline that acts via inhibition of cyclic adenosine monophosphate (cAMP) phosphodiesterase, resultantly interfering with megakaryocyte hypermaturation, leading to a dose-related reduction in megakaryocyte size, ploidy and maturation. The molecular basis of this activity on megakaryocytes is attributed to downregulation of GATA-1 and FOG-1 expression [19]. At markedly higher doses, ANA acts as an antiaggregant and was initially developed as an anti-coagulant [20]. ANA is a guideline-directed cytoreductive agent that has shown promise in the management of thrombocytosis in high-risk essential thrombocythemia (ET) [11–13].

The toxicity profile of ANA is best appreciated in the context of ET studies and includes cardiovascular (palpitations and arrhythmias, peripheral edema), gastrointestinal (diarrhea and abdominal pain), and neurological (headaches and dizziness) effects [21–23]. Studies in high-risk ET patients including PT-1 (n = 809), a randomized trial comparing HU plus aspirin to ANA plus aspirin, and EXELS (n = 3649), a non-randomized prospective study comparing ANA to other cytoreductive therapies with/without concomitant antiaggregant therapy, have demonstrated a significantly increased risk of progression to MF, hemorrhagic events, and arterial thrombosis in the ANA cohorts [22,24]. This is in contrast to ANAHYDRET, a smaller (n = 259) non-inferiority phase 3 randomized study in high-risk ET patients, that did not show a significant difference between treatment with ANA vs. HU in terms of associated thrombotic or serious hemorrhagic risk [25].

Although not part of guideline-directed PV therapy, ANA is often utilized in clinical practice as a platelet-lowering agent in the management of patients with PV with thrombocytosis; the safety and efficacy of this approach, however, has not been formally studied. The purpose of the present study was to utilize a well-established, large, multi-center database of patients with PV to retrospectively delineate the characteristics and outcomes of those patients who received ANA therapy.

2. Methods

2.1. Patients and outcomes

We utilized an established database of 527 patients with PV from 10 institutions throughout the Unites States as previously described [26]. For initial database inclusion, patients had to have been diagnosed with PV as defined by the 2016 World Health Organization (WHO) criteria, as well as to have been 18 years of age or older, and to have had at least three recorded hematologist appointments at their respective institution [27]. Institutional Review Board approval was attained at all centers prior to initiation of data collection, and research was conducted in accordance with the Declaration of Helsinki. Using this database, we retrospectively reviewed the deidentified data of 48 patients who had received ANA. High-risk PV was defined as age greater than or equal to 60 years and/or a history of prior thrombosis as per ELN criteria [9]. Extreme thrombocytosis was defined by platelets > 1500 $\times 10^9$/L.

HU resistance was defined as per the 2011 ELN guidelines as the presence of any one of the following criteria after three months of therapy with a minimum of 2 g/day HU: need for therapeutic phlebotomy to maintain hematocrit < 45%, uncontrolled myeloproliferation (peripheral blood platelet count > 400 $\times 10^9$/L and white blood cell (WBC) count > 10 $\times 10^9$/L), and/or failure to reduce palpable spleen length by 50% [9]. Adverse events that led to ANA dose reduction or discontinuation were derived on initial chart review at the time of database establishment from explicit provider documentation.

2.2. Statistical analysis

Patient characteristics were described at time of ANA initiation. Continuous variables were summarized as median (with interquartile range [IQR]) and categorical variables were summarized as number and percentage. Baseline laboratory values were defined as laboratory testing documented within 6 months prior to ANA initiation. Kaplan- Meier method was used to estimate the distribution of times to ANA discontinuation with median and corresponding 95% confidence intervals (95% C.I.) constructed based on the method of Brookmeyer and Crowley [28]. Hypothesis testing was two-sided and conducted at the 5% level of significance. All statistical analyses were done using SAS v9.4 (SAS Institute, Cary, NC).

3. Results

3.1. Patient characteristics

Among 527 patients, 48 (9.1%) received ANA therapy. Nine patients who were reported to have received ANA were excluded due to the absence of data regarding timing of ANA initiation and/or treatment duration, resulting in 39 patients included in the analysis (Fig. 1). Three patients initiated ANA therapy prior to the PV diagnosis but continued after the diagnosis was established, and thus were excluded from calculations of median time from PV diagnosis to ANA initiation, as well as from therapies attempted prior to ANA initiation. Six patients were excluded from the derivation of median initial ANA dose (five patients due to a missing initial dose, one patient due to a documented initial dose of 0 mg/day), and 5

patients from maximum daily dose (four patients due to missing dose, one due to a maximal dose of 0 mg/day).

Within the 39-patient cohort, the median age at time of ANA initiation was 63 years (IQR 52–72), including 18 (46.2%) females and 21 (53.8%) males. Twenty-seven (69.2%) of those patients who received ANA therapy had high-risk PV; this was based on both age and history of prior thrombosis in 8 patients, and age or thrombosis in an additional 17 and 2 patients, respectively (Table 1). No patients had extreme thrombocytosis prior to ANA initiation, nor did they have documented aVWD (Table 1). One patient had a single documented occurrence of extreme thrombocytosis two weeks after ANA initiation that resolved on repeat bloodwork less than four months later. All 39 patients harbored *JAK2V617F*, with no additional mutations detected (Table 1). Median peripheral blood counts at time of ANA initiation included platelets 682 × 10^9/L (IQR 481–774), hemoglobin 14.1 g/dL (IQR 12.1–14.9), hematocrit 44.1% (IQR 38.2–47.0), and WBC 9.9 × 10^9/L (IQR 7.3–15.2) (Table 2).

The baseline characteristics of those patients who did not receive ANA (n = 479) are described in Table S1. At time of initial presentation, their median age was 58 years (IQR 48–67), the prevalence of high-risk PV was 56.8%, and the median platelet count was 464 × 10^9/L (IQR 305–627). At diagnosis, ANA nonrecipients had a similar overall rate of prior thrombotic events to those who later received ANA therapy (Table 1, Table S1).

3.2. Therapy details

ANA was started at a median of 24 months (IQR 4–83) following PV diagnosis, at a median initial dose of 1.0 mg/day (IQR 0.5–1.5), and a median maximum dose of 1.5 mg/day (IQR 1.0–2.0) reached through the treatment course (Table 2).

While 20 patients (55.6%) had received HU therapy prior to ANA initiation, none had demonstrated resistance to HU. Additional therapies preceding ANA included peg-IFN-α−2a in three patients (8.3%) and IFN-alfa-2a in one patient (2.8%) (Table 2). MPN-directed treatments administered concomitantly with ANA included low-dose aspirin in 15 (38.5%), HU in 18 (46.2%), peg-IFN-α−2a in 4 (10.3%), and ruxolitinib in 7 (17.9%) patients (Table 2).

3.3. Outcomes

Overall, ANA was discontinued in 30 of 39 patients (76.9%), with a median time to discontinuation of 27.5 months (95% C.I. 12.0–49.2). A total of 62% (95% C.I. 0.48–0.80) and 38% (95% C.I. 0.25–0.60) of patients continued receiving ANA after 12 and 36 months, respectively (Fig. 2). While receiving ANA, three patients progressed to MF, and ANA was subsequently discontinued. An additional three patients had a documented cerebral vascular accident (CVA), all of whom continued receiving an unchanged dose of ANA.

ANA was dose-reduced in ten patients due to treatment-emergent adverse events (TEAEs) including palpitations (n = 4) and arrhythmias (n = 1), gastrointestinal complaints (n = 2), headaches (n = 1), and other/unknown causes (n = 2). Among the 30 patients in whom ANA was discontinued, reasons for discontinuation were documented in 21 patients; the

most frequent of these included palpitations (n = 5), cardiac arrhythmias (n = 2), nausea, vomiting, and/or diarrhea (n = 3), headaches (n = 2), severe bilateral lower extremity edema (n = 1), thrombocytopenia (n = 1), and lack of platelet response (n = 1) (Table 3). Of these, three patients had multiple documented reasons for discontinuation. Given the overall low event rates, time from ANA initiation to occurrence of TEAEs as detailed above could not be accurately depicted and thus not included.

Among those patients who had been receiving ANA therapy for at least one month and who had available bloodwork within the three months prior to ANA discontinuation (n = 23), the median platelet count at time of discontinuation was 293×10^9/L (IQR 230–604). The median platelet count within the four to eight months following ANA discontinuation was 416×10^9/L (IQR 311–629) (n = 23). Four patients developed thrombotic events following ANA discontinuation, including a myocardial infarction (MI) within one month (n = 1), a CVA after 34 months (n = 1), a deep venous thrombosis (DVT) after 10 years (n = 1), and renal vein and aortic thrombi greater than 11 years after discontinuation (n = 1).

A total of 12 patients were initiated on alternate therapies within two weeks of ANA discontinuation. Of these, seven were transitioned to HU, three to ruxolitinib, and two to peg-IFN-α−2a (one of whom was then switched to ruxolitinib within two months).

4. Discussion

ANA is a platelet selective cytoreductive agent included in evidence-based, consensus-driven guidelines for high-risk ET [5,9]. In the context of PV, however, data regarding the utility and safety of ANA is scarce. In this analysis, we sought to understand the patterns of ANA use and the associated outcomes within a large, multi-center database of patients with PV.

Overall, only a small proportion of patients—48 of 527—were treated with ANA (9 of whom were later excluded due to missing data). Within the 39-patient cohort, most patients had high-risk PV, and approximately a quarter had a history of prior arterial or venous thrombotic events (Table 1). None of the ANA-treated patients had a documented history of resistance to HU, extreme thrombocytosis, and/or aVWD. They also did not have other limiting cytopenias at the time of ANA initiation—with a median hemoglobin 14.1 g/dL (IQR 12.1–14.9) and WBC 9.9×10^9/L (IQR 15.12)—to explain the use of a platelet selective cytoreductive agent. The group of ANA nonrecipients demonstrated a trend toward a lower median platelet count and a lower prevalence of high-risk PV at time of initial presentation compared to ANA recipients at time of ANA initiation (data not shown); however, these represent distinct time points in PV disease course, and thus a direct comparison could not be made to support the use of ANA preferentially in the latter cohort. Moreover, no difference was noted between the two groups in terms of their overall rates of thrombotic events prior to diagnosis.

In line with prior studies of patients with MPNs [29], we found ANA to be effective in platelet reduction, from an initial median platelet count of 682×10^9/L (IQR 481–774) to a median platelet count of 293×10^9/L (IQR 230–604) at the time of ANA discontinuation.

The unresolved thrombocytosis in 10 of the 23 patients (43.5%) for whom bloodwork was present at the time of ANA discontinuation, however, may suggest further use of ANA was limited by tolerability. This study highlights a high rate of ANA discontinuation with a similar adverse event profile to that previously reported in the setting of ET, including cardiac complaints (arrhythmias and palpitations), gastrointestinal symptoms, and headaches in a significant number of patients (Table 3) [21–24]. Further, ANA therapy was not uniformly associated with thrombosis freedom as three patients developed arterial thromboses while receiving ANA. In comparison, only four patients developed thrombotic sequela following ANA discontinuation; in three, these events occurred approximately 3–11 years from the time of ANA discontinuation. Additionally, progression to MF was reported in three patients during ANA therapy, although a causal relationship could not be determined in this retrospective study.

These findings are not surprising in the context of prior studies of ANA use in ET. EXELS, a large, non-randomized prospective observational study of patients with high-risk ET (n = 3649) demonstrated increased rates of transformation to MF (HR 3.33, 95% C.I. 1.94–5.73; $p < 0.0001$) in ANA-treated patients when compared to patients who received other cytoreductive agents [22]. Similarly, a *post-hoc* multivariate analysis of EXELS that accounted for the substantial difference in median age between the ANA treatment group and other cytoreductive agents (56 vs. 70 years, respectively) had demonstrated an increased risk of overall major (HR 1.68, 95% C.I. 1.09–2.60; $p = 0.02$) and arterial thrombotic events (HR 1.91, 95% C.I. 1.20–3.04; $p = 0.0067$) in the ANA treatment group [22]. PT-1, a randomized trial comparing HU plus aspirin to ANA plus aspirin in 809 patients with high-risk ET, had also demonstrated increased rates of arterial thrombosis ($p = 0.004$) and progression to secondary MF ($p = 0.01$) with the latter [24]. Further, palpitations and tachyarrhythmias have been widely documented in prior ET studies in the setting of ANA use, postulated to be secondary to phosphodiesterase 3 inhibition and resultant positive inotropy and chronotropy; in a population predisposed to cardiovascular disease, these potential adverse effects are concerning [21–23,30]. A randomized phase 3b trial assessing the cardiac safety of ANA in high-risk ET (n = 150) did not show ANA-associated changes in left ventricular ejection fraction (LVEF), although we recognize this is only one surrogate marker of cardiotoxicity, and the study had low statistical power [31].

Moreover, while low-dose aspirin is a component of standard PV therapy regardless of risk categorization, interestingly only 15 of 39 patients in the current study received aspirin concurrently with ANA. This may be reflective of patients with unreported aVWD who were intentionally not treated with aspirin, and/or a concern for a synergistic effect between ANA and aspirin on platelet function. The decision to forego ASA in these cases may be influenced by a concern for increased hemorrhagic risk as shown in both the PT-1 study for ANA plus aspirin vs. HU plus aspirin (OR 2.61, 95% C.I. 1.27–5.33; $p = 0.008$), and the EXELS study for ANA plus antiaggregant vs. other cytoreductive therapy plus antiaggregant (HR 3.55, 95% C.I. 1.96–6.44; $p < 0.0001$) [22,24]. In contrast, the lack of significant difference in risk for hemorrhagic events between the ANA- and HU-treated groups in the smaller ANA-HYDRET study was likely at least partially attributable to the more restrictive use of aspirin in this study [25]. It is possible that the lack of documented serious

hemorrhagic events among the 39 ANA-treated patients in the current study is similarly reflective of the low rate of concomitant ASA therapy in this cohort.

Concerns regarding the tolerability of ANA are compounded by an absence of a clear benefit to targeting platelet count as a therapeutic goal in PV. Thrombocytosis has been shown to be associated with improved survival [17], decreased rate of disease progression, and lacking a clear association with risk of thrombosis in patients with PV [16]. A group-based trajectory model analysis of 440 patients with PV demonstrated a lack of a significant association between platelet count trajectories and thrombosis ($p = 0.9501$) or disease progression ($p = 0.1670$), and no significant association between hematocrit ($p = 0.1849$) or white blood cell (WBC) count ($p = 0.4163$) with thrombosis [26]. More recently, a study of 527 patients with PV receiving cytoreductive therapy showed that achievement of ELN response criteria —which mandates at least 12 weeks of peripheral blood count normalization and resolved splenomegaly [14]—was not associated with decreased risk of thrombosis ($p = 0.86$) nor death ($p = 0.80$). Further, when the impact of individual criterions was surveyed, a reduced hazard of progression was found to be driven mostly by peripheral WBC $< 10 \times 10^9$/L and absence of splenomegaly, whereas a normalized platelet count was associated with a considerably increased risk of disease progression (HR 2.70, 95% C.I. 1.26–5.80) [32]. Altogether, these findings suggest that a strict platelet goal should not be a therapeutic objective in the management of PV.

This study is innately limited due to its observational nature, and the resultant absence of a control group. Given this, while we describe hypotheses relating to our findings, no associations—causal or otherwise—can be drawn. Our study relies on the completeness and accuracy of the initial information entered into the database at each of the participating centers. Moreover, we are restricted to the information collected at that time, and are missing data that would have strengthened our understanding of ANA use and the reasoning for its utilization in this cohort. Our study is further limited by the relatively low prevalence of ANA use among patients with PV in the database. Given an overall low frequency of events among ANA-treated patients, we were also unable to perform a comparison analysis of outcome measures between the groups treated with ANA vs. other cytoreductive agents, or an adjusted analysis to definitively discern which of the concurrent therapies led to TEAEs.

Overall, the current study suggests that ANA represents an effective option for selective platelet control in patients with PV, albeit with a restrictive tolerability profile. The rates of thrombotic complications (7.7%) and treatment discontinuation due to toxicity (76.9%) in this cohort of PV patients treated with ANA were notable. This is compounded by current data indicating a lack of clear benefit in targeting a platelet goal as a therapeutic endpoint in PV. Rather, patients with PV may be better served by consistently pursuing thrombotic risk reduction with low dose aspirin when able, in order to target the PV-associated increase in thromboxane biosynthesis [7,33]. Pending large prospective studies assessing the role of ANA in PV, we suggest that platelet-directed cytoreduction be considered for patients with PV in the limited settings of extreme thrombocytosis with aVWD—given the associated hemorrhagic risk—and symptomatic thrombocytosis. Even in these instances, we advocate for the use of nonselective cytoreductive agents such as HU and IFN-α unless other

considerations such as a treatment-limiting anemia or leukopenia, non-hematologic toxicity, therapy resistance, or age and/or reproductive status influence treatment decisions.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Conflict of Interest

J.G. reports research grant funds for administration of clinical trials from Novartis, Blueprint Medicines, Deciphera, Cogent Biosciences; advisory board and honoraria from Blueprint Medicines, Novartis, Deciphera, Cogent Biosciences, Abbvie, and PharmaEssentia; reimbursement of travel expenses from Novartis, Blueprint Medicines. M.H. consults for and has received honoraria from CTI Pharma, Novartis, PharmaEssentia, and Blueprint Medicine; research funding from Blueprint Medicine, BMS, Cogent, CTI Pharma, Incyte, Kartos, and Sierra Oncology. A.K. reports consulting fees from Incyte; honoraria from PharmaEssentia and Imago; consulting and research fees from Protagonist. A.F. serves on the advisory board of CTI, PharmaEssentia, and Incyte. M.K. consults for and has received honoraria from Protagonist, Incyte and Constellation; research funding to the institution from Incyte, Constellation, Celgene and Protagonist. R.H. reports research support from Roche. J.M. reports clinical trial research support paid to the institution from Incyte, Novartis, CTI Bio, Geron, PharmaEssentia, AbbVie, BMS, Celgene, Roche, Kartos, Promedior, Merck; consultancy: Roche, Prelude, Sierra Oncology, Galecto, Incyte, Celgene, Kartos, Geron, CTI Bio, BMS, Constellation, Karyopharm, AbbVie, Imago, and PharmaEssentia.

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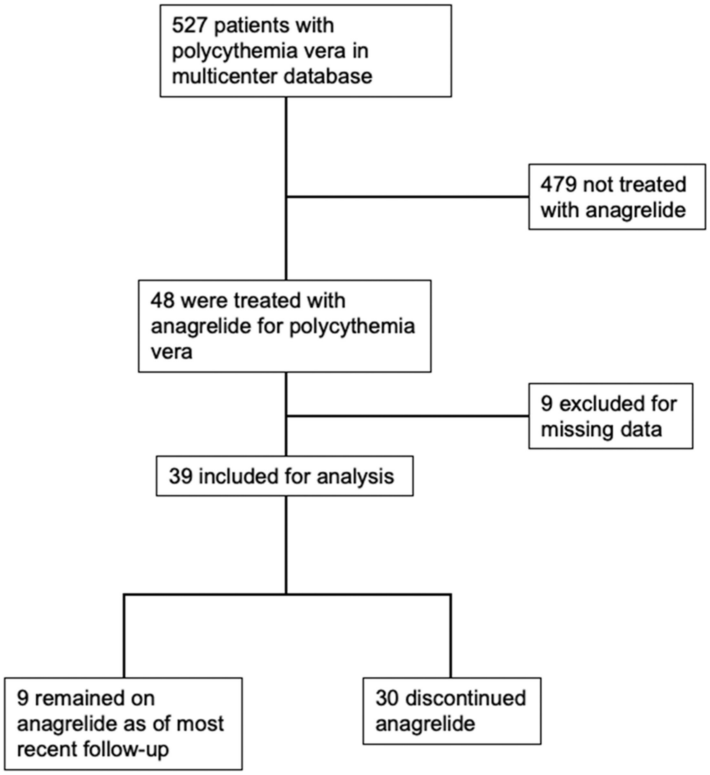

Fig. 1.
CONSORT diagram.

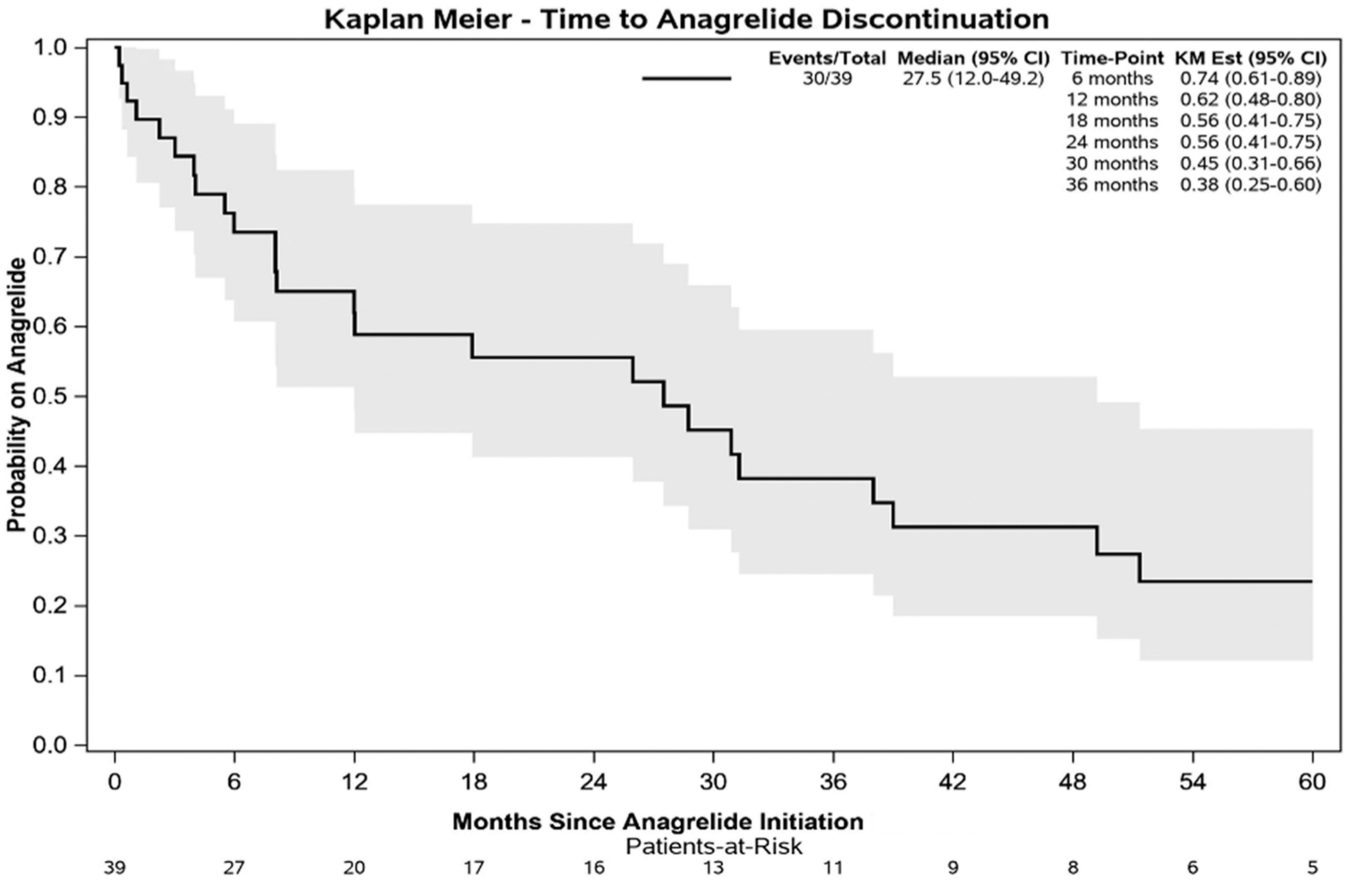

Fig. 2.

Kaplan-Meier curve of time to anagrelide treatment discontinuation.

Table 1

Baseline characteristics of anagrelide recipients

Parameter	Patients, N (%)
Age at anagrelide initiation (years), median (IQR)	63 (52–72)
Gender Female	18 (46.2)
Male	21 (53.8)
Ethnicity Asian	4 (10.3)
Black or African American	2 (5.1)
White	27 (69.2)
Other or unknown	6 (15.4)
Time from PV diagnosis to anagrelide initiation (months), median (IQR)[a]	24 (4–83)
High-risk PV patients (≥ 60 years old and/or history of prior thrombosis)	27 (69.2)
Prior history of venous thrombosis Deep vein thrombosis (DVT)[b]	7 (18.0) 3
Superficial thrombophlebitis Pulmonary embolism (PE)[b]	1 3
Prior history of arterial thrombosis	3 (7.7)
Cerebrovascular accident	2
Myocardial infarction	1
Extreme thrombocytosis[θ] prior to anagrelide	0 (0.0)
Acquired von Willebrand factor deficiency	0 (0.0)
Driver mutations *JAK2*V617F	39 (100.0)
JAK2 exon 12	0 (0.0)
CALR exon 9 insertion	0 (0.0)
*MPL*W515L/K	0 (0.0)
Triple negative or unavailable	0 (0.0)

Units as N (%) unless otherwise stated.

[θ] Platelets > 1500×10^9/L.

[a] 3 patients excluded given anagrelide initiation prior to PV diagnosis.

[b] 2 patients had a history of DVT / PE.

Table 2

Characterization of anagrelide therapy.

Parameter	Patients, N (%)
Peripheral blood counts at anagrelide initiation $^{\Phi}$	
Platelet count (x10^9/L), median (IQR)	682 (481–774)
Hemoglobin (g/dL), median (IQR)	14.1 (12.1–14.9)
Hematocrit (%), median (IQR)	44.1 (38.2–47.0)
White blood cell count (x10^9/L), median (IQR)	9.9 (7.3–15.2)
Therapies administered prior to anagrelide *	
HU	20 (55.6)
IFN-alfa-2a	1 (2.8)
PEGylated-IFN-alfa-2a	3 (8.3)
Combination treatment with anagrelide, N (%) Aspirin	15 (38.5)
Hydroxyurea	18 (46.2)
IFN-alfa-2a	0 (0.0)
PEGylated-IFN-alfa-2a	4 (10.3)
Ruxolitinib	7 (17.9)
Duration of anagrelide therapy (months), median	12 (4–39)
Initial anagrelide dose (mg/day), median (IQR) †	1.0 (0.5–1.5)
Maximum anagrelide dose (mg/day), median (IQR) $^{\Psi}$	1.5 (1.0–2.0)

Units as N (%) unless otherwise stated.

$^{\Phi}$Based on 20 patients for whom laboratory data was collected within the six months prior to anagrelide initiation.

*3 patients excluded given anagrelide initiation prior to PV diagnosis.

†6 patients excluded (5 patients due to a missing initial dose, 1 patient due to initial dose of 0 mg/day).

$^{\Psi}$5 patients excluded (4 patients due to missing dose, 1 due to a maximal dose of 0 mg/day).

Table 3

Precipitating events leading to anagrelide dose reduction or discontinuation.

Adverse events	Resultant anagrelide dose reduction, N (%)	Resultant anagrelide discontinuation, N (%)
Palpitations	4 (10.3)	5 (12.8)
Other/Unknown	2 (5.1)	25 (64.1)[a]
Nausea, vomiting, and/or diarrhea	2 (5.1)	3 (7.7)
Headaches	1 (2.6)	2 (5.1)
Arrhythmias	1 (2.6)	2 (5.1)
Weakness	0 (0.0)	2 (5.1)
Progression to myelofibrosis	0 (0.0)	3 (7.7)

[a]Including thrombocytopenia (n = 1) and bilateral lower extremity edema (n = 1).