The effect of eltrombopag in managing thrombocytopenia associated with tyrosine kinase therapy in patients with chronic myeloid leukemia and myelofibrosis

by Mahran Shoukier, Gautam Borthakur, Elias Jabbour, Farhad Ravandi, Guillermo Garcia-Manero, Tapan Kadia, Jairo Matthews, Lucia Masarova, Kiran Naqvi, Koji Sasaki, Srdan Verstovsek, and Jorge Cortes

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Mahran Shoukier,[1] Gautam Borthakur,[1] Elias Jabbour,[1] Farhad Ravandi,[1] Guillermo Garcia-Manero,[1] Tapan Kadia,[1] Jairo Matthews,[1] Lucia Masarova,[1] Kiran Naqvi,[1] Koji Sasaki,[1] Srdan Verstovsek,[1] Jorge Cortes[2].

[1] Department of Leukemia, the University of Texas MD Anderson Cancer Center, Houston, TX.

[2] Georgia Cancer Center at Augusta University (research performed while at MD Anderson Cancer Center).

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Corresponding Author:

Jorge Cortes, M.D.
Director, Georgia Cancer Center
Cecil F. Whitaker Jr., MD GRA Eminent Scholar Chair in Cancer
1410 Laney Walker Rd., CN2222
Augusta, GA 30912
Phone: 706-721-0570
jorge.cortes@augusta.edu

Word count: 2563

Number of Tables and Figures: Tables 4, Figure 1

Conflicts of Interest Disclosures

1. Mahran Shoukier: none

2. Gautam Borthakur: advisory board Novartis

3. Elias Jabbour: consultancy honoraria from BMS, Novartis, Pfizer, and Ariad

4. Farhad Ravandi: Honoraria and member of adcvisory board for Novarts

5. Guillermo Garcia-Manero: none

6. Tapan Kadia: Novartis- Honoraria

7. Jairo Matthews: none

8. Lucia Masarova: none

9. Kiran Naqvi: none

10. Koji Sasaki: none

11. Srdan Verstovsek: none

12. Jorge Cortes: research support from BMS, Novartis, Ariad, Chemgenex, and Pfizer.

Abstract

Approximately 20-50% patients with chronic phase chronic myeloid leukemia (CML-CP) treated with tyrosine kinase inhibitors (TKIs) or with myelofibrosis (MF) treated with ruxolitinib develop grade ≥3 thrombocytopenia needing treatment interruptions and dose reductions. We conducted a non-randomized, phase II, single-arm study to determine the efficacy of eltrombopag for patients with CML or MF with persistent thrombocytopenia while on TKI or ruxolitinib. Eltrombopag was initiated at 50 mg/day, with dose escalation up to 300 mg daily allowed every 2 weeks. Twenty-one patients were enrolled (CML=15, MF=6); median age 60 years (range, 31-97 years). The median platelet count was 44×10^9/L (range, $3\text{-}49 \times 10^9$/L) in CML and 62×10^9/L (range, $21\text{-}75 \times 10^9$/L) in MF. After a median of 18 months (range, 5-77 months), 12/15 patients with CML achieved complete platelet response. The median peak platelet count among responders was 154×10^9/L (range, $74\text{-}893 \times 10^9$/L). Among CML patients 5 could re-escalate the TKI dose and 9 improved their response. None of the 6 patients with MF had a sustained response. Therapy was generally well tolerated. One patient discontinued therapy due to toxicity (elevated transaminases). One patient with CML developed significant thrombocytosis ($>1000 \times 10^9$/L). Another CML patient developed non occlusive deep venous thrombosis in the right upper extremity without thrombocytosis, and one MF patient had myocardial infarction. Eltrombopag may help improve platelet counts in CML patients receiving TKI with recurrent thrombocytopenia. Further studies are warranted.

Introduction

Tyrosine kinase inhibitors (TKIs) are standard therapy for chronic myeloid leukemia (CML) and myelofibrosis (MF). Five TKIs are currently approved for the treatment of CML in various stages, namely imatinib, nilotinib, dasatinib, bosutinib and ponatinib. Although these agents are generally well tolerated, some patients may develop adverse events, with myelosuppression being the most prominent.[1-6] In most instances myelosuppression is grade 1 or 2 and requires no intervention. However, grade ≥3 thrombocytopenia (platelet ≤50x10^9/L) has been reported in 20% to 50% of patients. When this occurs, patients are usually managed with treatment interruption until platelets recovery (e.g., above 75x10^9/L) and dose reductions if thrombocytopenia recurs. Ruxolitinib is a JAK2 inhibitor used to manage splenomegaly and disease-associated symptoms in patients with MF.[7] The dose limiting toxicity of ruxolitinib was thrombocytopenia[8] and because of this the two pivotal phase 3 studies excluded patients with platelets ≤100x10^9/L. Still, thrombocytopenia was reported in 69% of patients, including 9% with grade ≥3.[9] In patients with platelet count of 50-100×10^9/L, grade ≥3 thrombocytopenia occurred in 56% of patients.[10] Ruxolitinib-associated grade ≥3 thrombocytopenia is also typically managed with dose reductions or interruptions.

Frequent dose interruptions and reductions might decrease TKI efficacy[11, 12] and may still not be sufficient to control thrombocytopenia. Patients who develop myelosuppression have a lower probability of achieving major or complete cytogenetic response (CCyR) [11]. For example, one study reported that patients treated with imatinib who developed grade ≥3 thrombocytopenia had a lower probability of CCyR compared to those who never developed thrombocytopenia (35% vs 59%, p=0.02, respectively).

Similarly, ruxolitinib efficacy is compromised with dose reductions and interruptions.[12, 13] To minimize dose reductions and interruptions, hematopoietic growth factors, filgrastim and erythropoietin stimulating agents (erythropoietin and darbepoetin) have been successfully used to manage neutropenia and anemia secondary to TKI in CML, respectively.[14, 15] Interleukin 11 (IL-11) was effective to manage thrombocytopenia associated with TKI in CML[16] but use of this agent is associated with significant adverse events including fluid retention and cardiac arrhythmias. Eltrombopag is a non-peptide thrombopoietin receptor agonist that is effective and well tolerated among patients with immune thrombocytopenia, chronic hepatitis C-associated thrombocytopenia and severe aplastic anemia.[17-19] It has also been safely used in acute myeloid leukemia without evidence of disease progression secondary to eltrombopag.[20] Here, we report the results from a pilot trial investigating the use of eltrombopag in the management of TKI- or ruxolitinib-associated thrombocytopenia among patients with CML and MF.

Methods

Patients

We conducted an open-label, non-randomized, phase II study of individualized dosing of eltrombopag. Eligible patients were aged 18 years or older with chronic phase CML receiving treatment with any FDA-approved TKI and experiencing Grade ≥3 thrombocytopenia (platelets ≤50x10^9/L), or with MF receiving ruxolitinib and with platelets <100x10^9/L (since it is a dose-limiting toxicity and a label threshold for ruxolitinib), in either case after the first three months of therapy.

Thrombocytopenia should have been either recurrent (i.e., be at least the second episode of thrombocytopenia) or have necessitated dose reductions of the TKI or ruxolitinib. All patients had signed an informed consent form approved by the institutional review board, and the study was conducted in accordance with the Declaration of Helsinki.

Study design

Eltrombopag was commenced at 50 mg with dose escalation allowed every 2 weeks to 100 mg, 150 mg, 200 mg, and 300 mg (a higher dose than per label considering the thrombocytopenia refractoriness on these patients and the intent to continue TKI/ruxolitinib) according to platelet response. Patients of East Asian ancestry, eltrombopag was commenced at 25 mg daily with dose escalation allowed every two weeks. The following guideline was used to adjust dosing of eltrombopag: if platelet count was $>200 \times 10^9$/L at any time, the daily dose was reduced by 25 mg and reassessed in 2 weeks; if $>400 \times 10^9$/L, therapy was withheld and platelets assessed twice weekly until platelet count $<150 \times 10^9$/L; therapy could then be resumed with the daily dose reduced by 25 mg. If platelet count $>400 \times 10^9$/L after 2 weeks at the lowest dose, therapy was permanently discontinued. TKI doses adjusted at the discretion of the treating physician per standard practice. Liver function tests (LFT's; alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin) was done before the initiation of eltrombopag, every 2 weeks during the dose adjustment phase and following the monthly establishment of a stable dose. When LFT abnormalities were identified, liver function tests were performed weekly until the abnormalities resolved or

stabilized; if ALT/AST levels were ≥3 times the upper limit of normal (ULN): therapy was withheld, we then repeated abnormal liver function tests within 3-5 days; if confirmed abnormal, we monitored LFT weekly until resolved, stabilized, or returned to baseline. If ALT/AST levels ≥3 times the ULN and were progressive, persistent (≥4 weeks), accompanied by increased direct bilirubin, or accompanied by clinical signs of liver injury or evidence of hepatic decompensation, eltrombopag was permanently discontinued. Patients who experienced other clinically significant grade 3 or greater toxicity possibly related to eltrombopag, had eltrombopag interruption until toxicity resolved to grade 1 or less. Treatment then was resumed at the immediate lower dose level. Failure to achieve a platelet count ≥50x10^9/L or ≥100x10^9/L in CML and MF patients, respectively after 8 weeks of eltrombopag was considered as lack of response.

Statistical analysis

Simon's optimal two-stage design [Simon, 1989] was used to test the null hypothesis that the proportion of subjects with complete response is ≤0.10 versus the alternative that it is ≥0.30 (i.e., Po≤0.10 vs Pa≥0.30) at alpha=0.05 with 80% power. The design resulted in an expected sample size of 15 and a probability of early termination of 0.736. The study was designed to study eltrombopag in 10 patients in the first stage; the trial would be terminated if 1 or fewer achieved complete platelet response. Otherwise, the trial would go to the second stage, and 29 patients would be studied. If the total number of patients with complete platelet response were less than or equal to 5, the drug would be deemed ineffective.

The MF group was an exploratory group of 10 patients to study the safety and activity of eltrombopag in patients with MF treated with Ruxolitinib. We considered the activity

promising if 3 or more patients out of 10 achieved complete platelet response. For safety monitoring in the cohort with MF, accrual would stop if, at any time, 4 out of 10 patients encounter grade 3 or more non-hematological toxicity or progression to acute leukemia. As an additional safety procedure, we observed the first 3 MF patients on trial for at least 3 months before other patients are accrued.

Response definitions

Complete platelet response was defined as platelet count ≥50x10^9/L for CML, and ≥100x10^9/L for MF that was sustained for ≥3 months while continuing TKI or ruxolitinib therapy or with sustained (≥3 months) re-escalation of TKI dose without recurrence of thrombocytopenia. Criteria for CML and MF response were previously defined[21, 22]. The target response was a complete response in at least 30% of patients.

Results

Twenty-one patients were enrolled: 15 with CML and 6 with MF. Their median age was 60 years (range, 31-97 years) and their clinical characteristics are shown in table 1. Median duration of disease was 2.2 years (range, 0.5-29 years) for patients with CML and 2 years (range, 0.3-3.6 years) for patients with MF. At the time of enrollment, patients with CML were receiving the following TKIs: dasatinib (n=5), ponatinib (n=4), nilotinib (n=3), bosutinib (n=2), and imatinib (n=1), 27% Were receiving their first TKI, 27% the 2nd TKI, 27% the 3rd, and 19% the 4th or later TKI. The median platelet count was 44x10^9/L (range, 3-49x10^9/L) in patients with CML and 62x10^9/L (range, 21-

$75x10^9$/L) in those with MF. Cytogenetic response for patients with CML at baseline were partial in 3, minor in 6, and none in 6. Prior therapies in MF patients were an investigational JAK2 inhibitor, and interferon alfa-2 in one patient each. The median dose of ruxolitinib was 10 mg [range, 10-30 mg] (Table 1). Eltrombopag dose distribution is summarized in Table 2.

After a median duration of treatment of 18 months (range, 5-77 months), 12 of the 15 (80%) patients with CML achieved a complete platelet response with doses of eltrombopag of 50–300 mg per day. The median peak platelet count among responders was $154x10^9$/L (range, $74-893x10^9$/L). The median time to best response was 6 months (range, 2.1-13 months). Ten patients had sustained platelet recovery after stopping eltrombopag. The median duration for sustained platelet response was 45 months (range, 3-69 months). The 3 patients who did not achieve a complete platelet response had only minor changes in platelet countwhile they were taking eltrombopag (from $3x10^9$/L to $8x10^9$/L, $19x10^9$/L to $45x10^9$/L, and from $42x10^9$/L to $46x10^9$/L, respectively).

Two patients (1 each of CML and MF) had improvement in hemoglobin of over 2 g/dl from baseline (from 8.2 g/dl to 10.6 g/dl, and from 9.4 g/dl to 11.4 g/dl, respectively), Hemoglobin improvement was sustained over 21.5 and 2 months respectively while patients were taking eltrombopag. Hemoglobin levels declined after interruption of eltrombopag. One patient with CML had absolute neutrophil count recovery to $>1x10^9$/L (baseline neutrophils $0.71x10^9$/L). Absolute neutrophil count improvement was sustained for >6 months while on eltrombopag. Absolute neutrophil count then declined

after interruption of eltrombopag. The TKI doses and duration for patient with CML post enrollment is summarized in table 1.

Nine patients with CML experienced an improvement in cytogenetic response during the observation period (all of them had sustained platelet recovery after stopping eltrombopag); one from none to complete, 2 from minor to complete, 4 from minor to partial, and 2 from partial to complete (Table 3). In 5 patients with CML the TKI's dose was increased and maintained while continuing eltrombopag. Dasatinib daily dose was increased from 50 mg to 100 mg in 3 patients, nilotinib dose was increased in one patient form 150 mg twice daily to 200 mg twice daily, and one patient had an increase in ponatinib dose from 15 every other day to 15 mg daily. There were no TKI dose-limiting toxicities in patients who increased their TKI doses. The dose increase was associated with improvement in CML response in 4 of these 5 patients. In the 5 CML patients who had a cytogenetic response but did not have TKI dose escalation, the improvement in cytogenetic response was noticed while patients were on eltrombopag. Three CML patients had switch in their TKI's (Supplemental Table). All 3 of these patients had already some improvement in thrombocytopenia before switching their TKI's, with the change indicated for other non-hematologic adverse events in one patient and the inefficacy of the TKI in the other two patients. None of the 6 patients with MF responded (i.e., none had a sustained increase in platelet count to $\geq 100 \times 0^9$/L); minor upward transient variations in platelet counts were seen in three patients (from 21×10^9/L to 28×10^9/L, 41×10^9/L to 55×10^9/L and from 65×10^9/L to 75×10^9/L, respectively).

As of the date of this report, 20 patients were off study because of lack of response (n=9), stem cell transplant (n=2), death (n=2), patient's wish (n=1), adverse events (n=2), TKI discontinuation (n=1), loss to follow up (n=1) and stable platelets (n=2). The two deaths on study were not related to treatment. One death was secondary to infectious complication in a patient with MF. The second death was secondary to hemorrhagic shock in a CML patient. This patient, treated with dasatinib, developed hepatosplenomegaly and ascites while on study but the etiology was not known. There was no evidence of portal vein thrombosis on CT abdomen/pelvis. Both eltrombopag and dasatinib were held and she had no platelets response. The platelet count was 10×10^9/L at the time of death due to severe gastrointestinal and genitourinary bleeding.

Therapy was well tolerated in most patients, but two patients on ponatinib developed thrombotic events. Two months after eltrombopag discontinuation due to termination of the study, one patient with CML developed significant thrombocytosis ($>`1000 \times 10^9$/L) with white blood cell count of 9.5×10^9/L, 3% basophils, and 2% peripheral blast accompanied by headache and eye pain. Ophthalmoscopic examination was suggestive of bilateral plaques or thrombosis in the retinal vasculature but fluoroscopic evaluation did not reveal retinal vasculature blockage. Ponatinib was discontinued and thrombocytosis was managed with hydroxyurea. The aforementioned symptoms resolved. There was no cytogenetic response prior or after starting eltrombopag. Seven months after stopping eltrombopag, the patient had persistent increase in blasts to 13%

without lack of hematologic response and she was then started on clinical trial with an investigational TKI. Another CML patient developed non occlusive deep venous thrombosis in the right upper extremity without thrombocytosis while on ponatinib 4 months after the study was terminated. One MF patient who had a history of coronary artery disease status post coronary artery bypass surgery developed myocardial infarction (MI) while on eltrombopag. This patent had then worsening increase in bone marrow fibrosis from grade 2 to grade 3 and was taken off study 40 days after MI. No further additional thrombotic/thromboembolic complications in CML and MF patients observed during or after the study. (Supplemental Table)

One patient (CML) discontinued therapy due to toxicity (elevation of liver function tests). Grade 3/4 toxicities irrespective of attribution listed in table 4. One patient with MF had increase in bone marrow fibrosis from grade 2 to grade 3. That patient had an increase in blast from 3% to 8% in the peripheral blood and from 1% to 6% in the bone marrow while he was on study but with an improvement in hemoglobin. There was no change in the patient's disease other than this change in blast percentage. The patient was taken off study for lack of platelet response and later started on another clinical trial (PRM-151 + ruxolitinib). No progression of disease has been documented in any other patients. No clonal evolution was observed in patients with prolonged eltrombopag use.

Discussion:

Thrombocytopenia is a common adverse event in patients with CML and MF who are treated with TKIs and ruxolitinib, respectively[10, 23]. In most instances, thrombocytopenia

is transient, occurs early during treatment initiation, and can be successfully managed with transient treatment interruptions and occasionally dose adjustments. However, in some patients thrombocytopenia can be persistent and more severe requiring frequent treatment interruptions and dose reductions, which might adversely influence treatment outcome[11]. To that end, rIL-11 was successfully used in CML patients for the management of TKI associated thrombocytopenia[16]. The main limitation of use of rIL-11 in the management of chemotherapy-induced thrombocytopenia in solid malignancies was the narrow therapeutic window with significant fluid retention and occasional arrhythmias. However, at lower doses used in CML, it was well tolerated[24, 25] with grade 1 or 2 peripheral edema observed in 6 patients (43%).

Eltrombopag is a 2nd generation oral thrombopoietin receptor agonist that has induced improvement of thrombocytopenia in patients with immune-mediate thrombocytopenia (ITP) or aplastic anemia. The EXTEND trial demonstrated that long-term use of eltrombopag was effective in maintaining for more than 6 months platelet counts of 50×10^9/L or more and reducing bleeding in most patients with ITP. Addition of eltrombopag to immunosuppressive treatment also markedly increased overall and complete hematologic response rates in treatment-naive severe aplastic anemia.[26] Here we describe the use of eltrombopag in the management of TKI-related thrombocytopenia in CML and MF. Our results suggest clinical benefit in most patients with CML with a generally favorable safety profile, although two patents (both on ponartinib) had thrombotic events. In contrast, no response was observed in patients with MF.

Theoretical concerns about the use of eltrombopag in this setting include increase in marrow blasts and possible transformation to advanced phases, thrombotic events including portal vein thrombosis, and increase in marrow fibrosis. We did not observe any instance of transformation in our series, in concordance with pre-clinical and clinical data showing no evidence of worsening leukemia[20, 27]. There was also no increase in marrow fibrosis in CML patients. Our series is small so the lack of such events should be considered as preliminary but reassuring. The most common adverse event was liver function test elevation, but these were generally transient, reversible and manageable with dose adjustments. However, in one case it led to discontinuation of eltrombopag because of recurrent transaminitis. Two patients who received ponatinib (50%) had thrombotic events while on eltrombopag, this might raise the precaution of using ponatinib in conjunction with eltrombopag in CML patients.

Despite the median disease duration of 2.2 years and multiple TKIs use in CML patients before enrollment, eltrombopag demonstrated clinical efficacy with complete platelet response of 80% (12/15). This compares favorably to what was reported with rIL-11[16]. More important, 9 patients (60%) had improvement in cytogenetic responses, likely the result of a more sustained therapy with TKI. Notably, as doses of eltrombopag were increased, LFT elevations were noted in some patients. Conversely, eltrombopag dose interruptions or reductions due to such events or to platelets reaching >200 x 10^9/L, occasionally resulted in a drop-in platelet counts. Thus, close monitoring and dynamic management is required, at least during the initial stages of therapy to obtain the maximum effect while maintaining safety. The lack of efficacy among patients with MF

could be in part secondary to advanced disease, or possible antagonism between the two medications. Thrombopoietin agonist are dependent on JAK-stat pathway which is inhibited by ruxolitinib[28].

Our study has several limitations. It was a small study, and it did not accrue to the target sample size of 29 patients due to slow enrollment making the observation preliminary and requiring confirmation. We also do not have evidence or investigation of any immune mechanisms associated with thrombocytopenia, although we believe it is unlikely that these patients with CML had an immune mediated thrombocytopenia, and uncommon occurrence in this setting.

In conclusion, our findings show that eltrombopag doses up to 300 mg may alleviate TKI-associated thrombocytopenia in some patients with CML. No similar benefit has been observed in patients with MF treated with ruxolitinib. Although generally safe, thrombotic events were noted that deserve further investigation, particularly when used in combination with ponatinib. Additional studies are warranted to confirm these observations.

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Table 1. Baseline Characteristics

Characteristics	N (%)	Median [range]
Age, years		60 [31-97]
Male	12 (58)	
Disease		
CML	15 (71)	
MF	6 (29)	
Stage of CML at start of eltrombopag		
Chronic phase	15 (100)	
Disease duration prior to Eltrombopag initiation (years)		
CML		2.2 [0.5-29]
MF		2 [0.3-3.6]
Hemoglobin (all patients), g/dl		11.6 [8.2-13.4]
WBC (all patients), $\times 10^9$/L		4.6 [1-71.3]
Platelet count (CML), $\times 10^9$/L		44 [3-49]
Platelet count (MF), $\times 10^9$/L		62 [21-75]
TKI (CML patients)		dose mg/d
Dasatinib	5 (33)	50 [50-100]
Ponatinib	4 (27)	11.25 [7.5-30]
Nilotinib	3 (20)	300 [150-600]
Bosutinib	2 (13)	300
Imatinib	1 (7)	400
Ruxolitinib (MF patients)	6 (100)	10 [10-30]
Time on TKI before eltrombopag, years		2.1 [0.5-14]
Time on ruxolitinib before eltrombopag, months		3 [3-18]
Cytogenetic response prior to eltrombopag (CML)		
None	6 (40)	
Minor	6 (40)	
Partial	3 (20)	

CML: chronic myeloid leukemia; MF: myelofibrosis; TKI: tyrosine kinase inhibitor. TKI

was on hold in 6 patients with CML at time of enrollment because of grade 3 thrombocytopenia.

Table 2. Eltrombopag dose distribution mg/d (all patients)

Dose	N (%)	
	Maximum dose	**Dose at last follow up**
0	0	2 (10)
25	1 (5)	0
50	3 (14)	3 (14)
100	0	3 (14)
150	2 (10)	2 (10)
200	2 (10)	1 (5)
275	0	1 (5)
300	13 (61)	9 (42)

Table 3. Response to Eltrombopag in CML patients

Cytogenetic response (CML patients)		
Before eltrombopag	**On eltrombopag**	**No.**
None	Complete	1
Minor	Complete	2
Minor	Partial	4
Partial	Complete	2
TKI median percentage of standard dose		
Before Eltrombopag	**On eltrombopag**	**P value**
55	73.5	0.3

CML: chronic myeloid leukemia; TKI: tyrosine kinase inhibitor.

Table 4. Treatment Emergent Adverse Events

Event	No. (%)	
	Any	**Grade 3-4**
Elevated AST/ALT	9 (16)	5 (22)
Fatigue	7 (12)	2 (8)
Infection	7 (12)	6 (25)
Diarrhea	4 (7)	1 (5)
Rash	3 (5)	-
Insomnia	3 (5)	-
Hyperglycemia	2 (4)	2 (8)
HTN	2 (4)	2 (8)
HLD	2 (4)	2 (8)
Pleural effusion	2 (4)	1 (4)
Headache	2 (4)	-
Hyperbilirubinemia	2 (4)	-
Limb edema	2 (4)	-
Blurred vision	2 (4)	-
Peripheral neuropathy	2 (4)	-
Thrombocytosis	1 (2)	1 (4)
Chest pain	1 (2)	1 (4)
Myocardial infarction	1 (2)	1 (4)
Periorbital edema	1 (2)	-
Non occlusive deep venous thrombosis	1 (2)	

Figure legend

Figure 1 Platelet change from baseline to response.

*Each blue bar reflects change in platelet count in a CML patient, while each green bar reflects change in platelet count in a MF patient.

Platelet Change from Baseline to Response

MFIB
CML

Change in platelet count from baseline to best response, x10^9/L
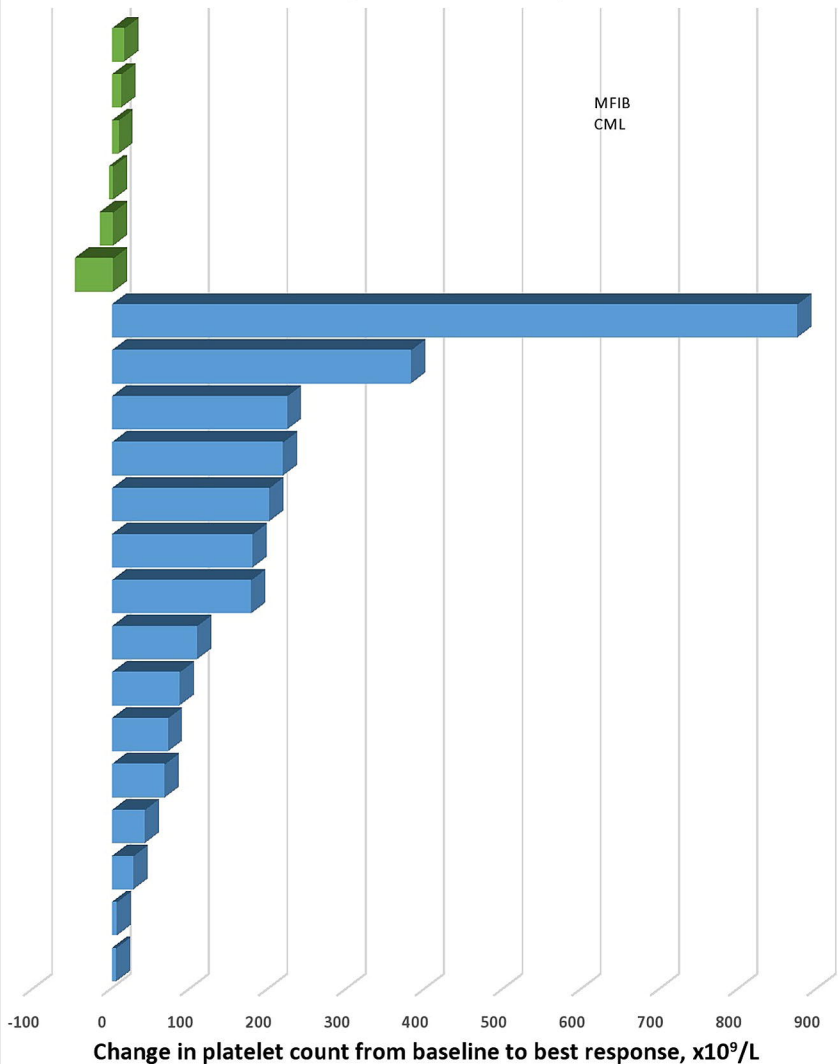
N	Baseline PLT count x x10^9/L	Best PLT count x10^9/L	TKI line	TKI	TKI dose mg before eltrombopag	TKI at last follow - up	TKI dose mg at last follow - up	Duration of eltrombopag months	Response
1	34	210	2	dasatinib	50	dasatinib	100	77	CCyR
2	29	123	1	dasatinib	100	nilotinib	400	18	None
3	47	174	3	dasatinib	50	dasatinib	100	19	Partial
4	34	106	1	nilotinib	600	ponatinib	30	17	Partial
5	48	265	4	ponatinib	7.5	ponatinib	15	63	CCyR
6	49	248	4	ponatinib	7.5	ponatinib	7.5	17	None
7	48	133	3	bosutinib	300	bosutinib	300	62	Partial
8	44	424	5	bosutinib	300	bosutinib	300	12	Partial
9	49	227	3	dasatinib	50	dasatinib	100	51	CCyR
10	37	259	2	imatinib	400	dasatinib	100	48	CCyR
11	20	893	2	nilotinib	300	nilotinib	400	38	CCyR
12	19	163	1	ponatinib	15	ponatinib	15	8	None
13	42	93	1	dasatinib	70	dasatinib	70	5	None
14	39	1225	3	ponatinib	30	ponatinib	30	6	None
15	3	12	2	nilotinib	150	nilotinib	150	5	None

Plt: platelets; **TKI:** tyrosine kinase inhibitor.