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

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ABSTRACT

Approximately 20-50% patients with chronic phase chronic myeloid leukemia (CML-CP) treated with tyrosine kinase inhibitors (TKI) 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); with a median age of 60 years (range, 31-97 years). The median platelet count was $44x10^9$/L (range, $3-49x10^9$/L) in CML and $62x10^9$/L (range, $21-75x10^9$/L) in MF. After a median of 18 months (range, 5-77 months), 12 of 15 patients with CML achieved complete platelet response. The median peak platelet count among responders was $154x10^9$/L (range, $74-893x10^9$/L). Among CML patients five could re-escalate the TKI dose and nine improved their response. None of the six 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 (>$1,000x10^9$/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 (clinicaltrials gov. Identifier: NCT01428635).

Introduction

Tyrosine kinase inhibitors (TKI) are standard therapy for chronic myeloid leukemia (CML) and myelofibrosis (MF). Five TKI 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 III 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 a platelet count of 50-

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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] In order 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 Food and Drug Administration-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 3 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. For patients of East Asian ancestry, eltrombopag was commenced at 25 mg daily with dose escalation allowed every 2 weeks. The following guideline was used to adjust dosing of eltrombopag: if the platelet count was >200x10^9/L at any time, the daily dose was reduced by 25 mg and re-assessed in 2 weeks; if >400x10^9/L, therapy was withheld and platelets assessed twice weekly until platelet count <150x10^9/L; therapy could then be resumed with the daily dose reduced by 25 mg. If the platelet count >400x10^9/L after 2 weeks was at the lowest dose, therapy was permanently discontinued. TKI doses were adjusted at the discretion of the treating physician per standard practice. Liver function tests (LFT) (alanine aminotransferase [ALT], aspartate aminotransferase [AST], and bilirubin) were 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, LFT were performed weekly until the abnormalities resolved or stabilized; if ALT/AST levels were ≥ three-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 ≥ three-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 ten patients in the first stage; the trial would be terminated if one 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 five, the drug would be deemed ineffective.

The MF group was an exploratory group of ten patients to study the safety and activity of eltrombopag in patients with MF treated with ruxolitinib. We considered the activity promising if three or more patients out of ten achieved complete platelet response. For safety monitoring in the cohort with MF, accrual would stop if, at any time, four of ten patients encounter grade 3 or more non-hematological toxicity or progression to acute leukemia. As an additional safety procedure, we observed the first three MF patients on trial for at least 3 months before other patients were 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 six with MF. Their median age was 60 years (range, 31-97) 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 TKI: dasatinib (n=5), ponatinib (n=4), nilotinib (n=3), bosutinib (n=2), and imatinib (n=1), 27% were receiving their first TKI, 27% the second TKI, 27% the third, and 19% the fourth 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 three, minor in six, and none in six. Prior therapies in MF patients were an investigational JAK2 inhibitor, and interferon α-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 three patients who did not achieve a complete platelet response had only minor changes in platelet count while 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 (one 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 an 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 patients with CML post enrollment are summarized in Table 1.

Nine patients with CML experienced an improvement in the cytogenetic response during the observation period (all of them had sustained platelet recovery after stopping eltrombopag); one from none to complete, two from minor to complete, four from minor to partial, and two from partial to complete (Table 3). In five patients with CML the TKI dose was increased and maintained while continuing eltrombopag. Dasatinib daily dose was increased from 50 mg to 100 mg in three 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 mg 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 four of these five patients. In the five 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 a switch in their TKI (*Online Supplementary Table S1*). All three of these patients had already some improvement in thrombocytopenia before switching their TKI, 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 six patients with MF responded (i.e., none had a sustained increase in platelet count to ≥100x10^9/L); minor upward transient variations in platelet counts were seen in three patients (from 21x10^9/L to 28x10^9/L, 41x10^9/L to 55x10^9/L and from 65x10^9/L to 75x10^9/L, respectively).

As of the date of this report, 20 patients were off study because of a 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)

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), x10^9/L		4.6 [1-71.3]
Platelet count (CML), x10^9/L		44 [3-49]
Platelet count (MF), x10^9/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 six patients with CML at time of enrollment because of grade 3 thrombocytopenia; WBC: white blood cells.

Table 2. Eltrombopag dose distribution, mg per day (all patients).

	N (%)	
Dose	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)

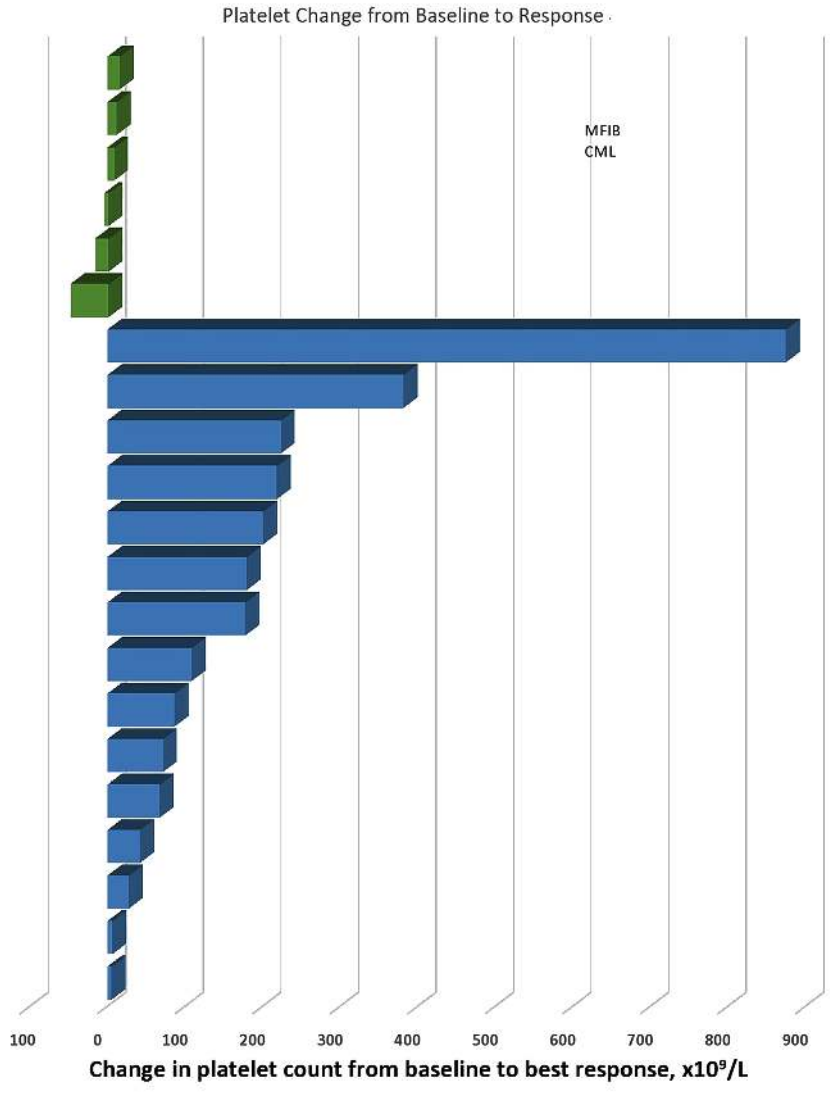

Figure 1. Platelet change from baseline to response. *Each blue bar reflects change in platelet count in a chronic myeloid leukemia patient, while each green bar reflects change in platelet count in a myelofibrosis patient.

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 $10x10^9$/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 (>$1,000x10^9$/L) with a white blood cell count of $9.5x10^9$/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 a persistent increase in blasts to 13% without a lack of hematologic response and she was then started on a 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 (*Online Supplementary Table S2*).

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 an 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 an increase 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 + ruxoli-

tinib). 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 TKI 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 six patients (43%).

Eltrombopag is a second 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 LFT 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 TKI use in CML patients before enrollment, eltrombopag demonstrated clinical efficacy with complete platelet response of 80% (12 of 15). This compares favorably to what was reported with rIL-11.[16] More important, nine 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 $>200x10^9$/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

Table 3. Response to eltrombopag in chronic myeloid leukemia 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*
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)	

ALT: alanine aminotransferase; AST: aspartate aminotransferase; HTN: hypertension; HLD: hyperlipidemia.

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.

Disclosures

MS, GG-M, JM, LM, KN, KS, and SV have no conflicts of interset to disclose; GB sit on the advisory board of Novartis; EJ has received consultancy honoraria from BMS, Novartis, Pfizer, and Ariad; FR has received honoraria and is a member of the advisory board of Novarts; TK has received honoraria from Novartis; JC has received research support from BMS, Novartis, Ariad, Chemgenex, and Pfizer.

Contributions

MS analyzed the data, and wrote the paper; GB designed, and performed research; JM performed research, and analyzed the data; JC designed, performed research, analyzed the data, and wrote the paper; and all authors contributed to data collection, reviewed and approved the manuscript, and shared final responsibility for the decision to submit.

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