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Severe thrombocytopenia in myelofibrosis is more prevalent than previously reported

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To the Editor,

Since the FDA and EMA approval of ruxolitinib in 2011 and 2012 respectively, JAK2 inhibition has revolutionized symptomatic control of myelofibrosis (MF) and improved overall survival [1]. Recently a second JAK2 inhibitor, fedratinib, has been approved with a similar indication in MF. However, neither of these latter agents have been well studied in patients with severe thrombocytopenia (platelet count < 50,000/μL), and neither has a recommended starting dose for such patients. Although this population represents an area of serious unmet medical need, the prevalence of such patients is not well characterized. To facilitate treatment development, it is critical to determine the size of this understudied population.

Thrombocytopenia is a known adverse prognostic factor in patients with MF. Those with severe thrombocytopenia fair the worst, with the highest rates of anemia, transfusion dependency, higher peripheral blast counts, greater risk of leukemic progression, and shortest survival (median overall survival for patients with platelets < 50,000/μL is 15 months versus 44 months for those with platelets 50,000–100,000/μL and 57 months with platelets > 100,000/μL; $P < 0.001$) [2]. Moreover, MF patients with thrombocytopenia experience greater symptomatic burden than those without thrombocytopenia [3]. Additionally, current treatment options have not been studied in these patients, and they are often excluded from clinical studies. Several publications have presented the incidence of severe thrombocytopenia at presentation or diagnosis as 11–16% [4,2,5]. However, incidence-based modeling does not account for patients who develop severe thrombocytopenia due to either treatment-related reductions or the natural course of the disease. Additionally, thee published data rely heavily on data from academic centers where there may be a bias towards patients earlier in their disease course fit enough to travel. In

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LM and JH interpreted data and drafted the manuscript. JAT interpreted data and edited manuscript. RM contributed to and edited the manuscript.

order to estimate the prevalence of severe thrombocytopenia in patients with MF, a series of surveys were conducted with hematologists/oncologists across several countries.

Three independent 30-minute internet surveys were conducted between April 2017 and June 2018. Survey 1 (n = 154) was conducted in 5 European countries (DE, ES, FR, GB, IT), Survey 2 (n = 253) in same 5 European countries plus the US, and Survey 3 (n = 400) was conducted in 12 countries/regions (AU, CA, DE, ES, FR, GB, IL, IT, JP, KR, US, and the Nordics). Eligibility requirements for all surveys included having a specialty of medical oncology, clinical oncology, hematology/oncology, or hematology; primarily practice in an academic or community-based setting; spends > 50% of their time in the clinical practice setting; have been in practice for 3–30 years (up to 35 years in JP or KR); treated ≥ 5 symptomatic MF patients in the prior year (≥ 2 if in AU, JP, KR, or Nordics); and passed standard screening criteria. Physicians were asked: “Of your myelofibrosis patients in the past 12 months, how many fell into the following platelet groups at their last treatment initiation? < 50,000/μL; 50–100,000/μL, and > 100,000/μL.”

A total of 807 physicians from 12 countries (60% EU, 25% US, 15% ex-US/EU) completed the surveys, 54% from academic centers and 46% from community-based centers. Overall, physicians reported a prevalence of 35% with severe thrombocytopenia in their MF patients (34%, 36% and 34% in the three surveys respectively). In addition, they reported a prevalence of 34% for patients with platelets 50–100,000 and 32% for those with platelets > 100,000/μL. Results were similar between the US and EU, with 36% and 35% of patients having platelet counts < 50,000/μL; 33% and 35% having platelet count 50–100,000/μL, and 31% and 30% having platelet counts > 100,000/μL, respectively. Ex-US/EU countries reported 29% of their patients had severe thrombocytopenia, 32% had platelet counts 50–100,000/μL, and 39% had platelet counts > 100,000/μL. Prevalence was similar between academic and community physicians and across regions.

This is the first known international study aimed at estimating the prevalence of severe thrombocytopenia in patients with MF, involving over 800 physician surveys. These data demonstrate that patients with severe thrombocytopenia comprise approximately one-third of the prevalent MF population, a significantly higher percentage than that estimated in incidence-based studies that fail to account for worsening platelet counts during the disease course due to either drug toxicity or disease progression. By nature of this being a survey-based study, results may be subject to recall bias. There are approximately 18,000 MF patients in the US and 24,000 in the EU, our results predict 6000 and 8000 of the MF patients will experience severe thrombocytopenia during their disease course in the US and EU respectively, versus only 2000 and 2600 patients respectively utilizing an incidence-based estimate. These results indicate there is a larger population of patients with this serious unmet medical need than previously recognized.

Declaration of Competing Interest

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