Splenomegaly impacts prognosis in essential thrombocythemia and polycythemia vera: A single center study

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Abstract

Splenomegaly is one of the major clinical manifestations of primary myelofibrosis and is common also in other chronic Philadelphia-negative myeloproliferative neoplasms, causing symptoms and signs and affecting quality of life of patients diagnosed with these diseases. We aimed to study the impact that such alteration has on thrombotic risk and on the survival of patients with essential thrombocythemia and patients with Polycythemia Vera (PV). We studied the relationship between splenomegaly (and its grade), thrombosis and survival in 238 patients with et and 165 patients with PV followed at our center between January 1997 and May 2019.

Introduction

The 2016 revision of the WHO *Classification of Tumors of Hematopoietic and Lymphoid Tissues* includes new criteria for the diagnosis of Philadelphia-negative myeloproliferative neoplasms (MPNs). This revision includes Polycythemia Vera (PV), Essential Thrombocythemia (ET), and Primary Myelofibrosis (PMF), distinguished in overt and prefibrotic PMF.[1]

Splenomegaly is one of the major clinical manifestations of PMF. Progressive splenomegaly is significantly associated with debilitating symptoms, such as early satiety, abdominal pain, inactivity and fatigue and may cause portal hypertension and progression of cytopenias due to splenic sequestration.[2] The symptoms linked to splenomegaly are associated with its grade, but it may also be asymptomatic. In one study, palpable splenomegaly was observed in 80% of the asymptomatic patients and about 10% of the patients with PMF showed severe symptomatic splenomegaly when diagnosed with PMF.[3] The role of splenomegaly on quality of life and on prognosis in patients with PMF is fairly well known,[4] instead the impact of splenomegaly in essential thrombocythemia and polycythemia vera is less investigated.

A mild to moderate spleen enlargement is present in about 5-20% of ET patients at diagnosis. Notwithstanding the relatively common occurrence of this feature, the prognosis of patients with spleen enlargement in ET is still unclear.[5] PV is a chronic clonal myeloproliferative neoplasm characterized by increased red-cell mass; elevated white cell and platelet counts are also commonly observed in PV. PV patients have an increased risk of thrombotic and cardiovascular events and a burden of symptoms that often includes pruritus, fatigue, and night sweats.[6] In a single center study with 587 patients diagnosed with PV, 155 of 506 with available data (31%) had palpable splenomegaly at diagnosis and it was associated with a higher risk of developing venous thrombosis during follow-up.[7] Splenomegaly often develops at disease progression in approximately 30-40% of patients with PV.[8,9]

Despite the clinical relevance, increased spleen size has not been proven as a significant prognostic factor in the elaboration of major prognostic models commonly used to estimate survival, including International Prognostic Scoring System (IPSS), Dynamic IPSS (DIPSS), Dynamic IPSS plus (SIPSS-plus), MF Secondary to PV/ET-Prognostic Model (MYSEC-PM) and Mutation-enhanced IPSS70 (MIPSS-70) in patients with MF, in risk stratification for survival in patients with PV and ET,[10-14] and in traditional stratification for thrombotic risk for ET and PV,[15] in International Prognostic score of thrombosis (IPSET-thrombosis, and in revised international prognostic scoring system for essential thrombocythemia.[16,17]

In relation to the frequency and clinical relevance of splenomegaly in patients with ET or PV, we aimed to study the impact that such alteration has on thrombotic risk and on the survival of these patients.

Materials and Methods

From January 1997 to May 2019, 238 consecutive patients with diagnosis of ET and 165 patients with PV were followed at our center. Diagnosis were all made according to WHO criteria used in the respective period. The frequency of splenomegaly at diagnosis was calculated considering it positive if minimum longitudinal diameter was 15 cm at echotomography of computed tomography and was evaluated in groups of patients with diagnosis of PMF, PV and ET. Clinical features, driver-gene mutational status, age and sex were collected for all the patients with ET and PV. The frequency of thrombosis or cardiovascular events in the groups with and without splenomegaly and the number of deaths in the two groups were studied and survival was estimated using the Kaplan and Meier method. Comparison between frequencies is performed with chi-square test, comparison between medians with the Kruskal-Wallis test, while comparison between survivals using the log-rank test.

Results

In our study, 238 patients with ET and 165 with PV were followed along more than 22 years at our institution, with a median follow-up of 45.96 months (1.5-316.2) for ET patients and 58.42 months (1.2-298.39) for PV patients. The median age was respectively 65.92 years (14.56-92.09) and 62.28 (17.4-93.44). They were diagnosed according to WHO criteria used in the respective period.

Data on the driver-gene mutational status revealed that, between ET patients, 172/238 (72.26%) were JAK2V617F positive, 23/238 (9.66%) were CALR mutated and 4/238 (1.68%) were MPL mutated,

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while 39/238 (16.38%) were triple-negative; among PV patients, 156/165 (94.54%) were JAK2V617F positive, 5/165 (3,03%) harbored mutation on JAK2 exon 12 and 4/165 (2,42%) were negative for JAK2 mutations;

According to diagnosis subgroups, splenomegaly was present respectively in 15,54% of patients with ET and in 38.18% of PV patients. Table 1 shows gender and median age in patients with or without splenomegaly distinguished by type of MPNs. Our data show the presence of splenomegaly in 24% of males and 11.65% of females with ET, while showing splenomegaly in 45.71% of males and in 24.19 of females with PV.

The frequency of thrombosis or cardiovascular events appears to be higher in patients with splenomegaly than in patients without splenomegaly at diagnosis, both in patients with ET and in patients with PV. In fact, they occur in 39.87% of patients with ET and with splenomegaly towards 24.37% of patients without splenomegaly (P=0.04). In patients with PV thrombosis or cardiovascular events occurred in 44.44% of patients with splenomegaly and in 30.39% of patients without splenomegaly (P=0.02)

Table 1. Age and sex in patients with myeloproliferative disease with or without splenomegaly.

	Age (median)	Sex (m/f)
Essential thrombocythemia	65,92	75/163
Splenomegaly	67,94	18/19
No splenomegaly	65,85	57/144
Polycythemia vera	62,28	103/62
Splenomegaly	60,55	48/15
No splenomegaly	62,48	55/47

In patients with splenomegaly at diagnosis we found a higher number of deaths compared to patients who did not present splenomegaly both in ET and PV patients, and respectively 32.43% *versus* 8.42% (P=0.0001) and 22.22% *versus* 7.84% (P<0.004). Finally, survival in patients presenting with splenomegaly at diagnosis appears significantly worse, as it can be seen in Figure 1.

Discussion and Conclusions

Splenomegaly is one of the most common manifestations among those present at diagnosis of MPNs. In our experience, splenomegaly is can be revealed in about 15.54% of patients with ET an 38.18% of PV patients at diagnosis. Furthermore, our data show an important correlation with the thrombotic risk, with the frequency of deaths and with survival.

Ruxolitinib, an oral JAK1/JAK2 inhibitor, is approved for the treatment of patients with IPSS intermediate or high-risk PMF and patients with PV who have had an inadequate response to or are intolerant to hydroxyurea. Ruxolitinib has been shown to be effective in reducing splenomegaly both in patients with PMF and in patients with PV,[18-20] significantly improving the life quality of the patients. Current therapies available for ET do not significantly affect splenomegaly.

Despite the clinical relevance, increased spleen size has not been proven as a significant prognostic factor in major prognostic models. In accordance with our data and our experience, we believe that the prognostic value of splenomegaly is underestimated in ET and PV and that should be evaluated the possibility to include it as an item of a prognostic scoring system. Further well-designed clinical studies are needed to evaluate the significance of splenomegaly in ET and PV patients and its impact on overall survival and on thrombotic risk.

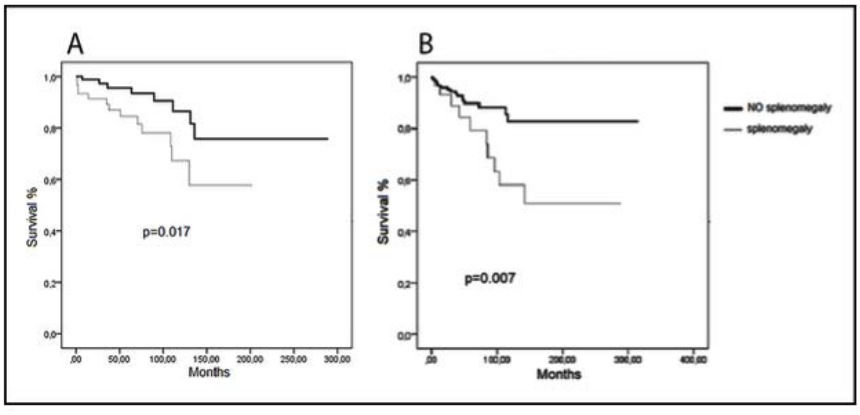

Figure 1. Survival in patients with splenomegaly versus patients without splenomegaly at diagnosis. In PV patients (A) and ET patients (B).

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