Patients With Prefibrotic Myelofibrosis and Inferior Outcome, a Single-Center Analysis

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Abstract

CONTEXT: The 2016 WHO classification distinguishes prefibrotic primary myelofibrosis (pre-PMF) as separate entity. PMF differs from overt MF by lesser degree of marrow fibrosis: only grade 0-1; and confers favorable survival.

OBJECTIVE: To characterize pre-PMF patients referred to our institution between the years of 2000-2020 and identify patients with the worst outcome.

PATIENTS and DESIGN: Retrospective study of 130 newly diagnosed pre-PMF patients with available marrow fibrosis grading. IPSS scores and individual factors used in IPSS were annotated (Cervantes, et al. Blood. 2009),

MAIN OUTCOMES: Overall survival (OS) of patients according to IPSS risks as well as presence of individual IPSS risk factors: i) hemoglobin < 10 g/dL; ii) WBC > 25 x109/L; iii) peripheral blasts ≥1%, in the context of age > 65 years and +/- systemic symptoms (Kaplan-Meier analysis with log rank test).

RESULTS: Majority of patients had grade 1 fibrosis (88%). Total of 58 patients (45%) had intermediate 2 or high risk IPSS. Twenty-seven percent, 24% and 11% of patients had none, one and two i-iii) factors. Patients with no i-iii) factors but symptoms were in 38%.

Median OS of the entire cohort was 68 months (95% CI 42-94). Overall survival (95% CI) per IPSS: low-intermediate 1 and 2 - high were not reached, 179 months (65-not expressed), 65 months (32-98) and 27 months (5-49), respectively. Median OS (95% CI) of patients without i-iii) factors +/- symptoms was not reached. Median OS of patients with one i-iii) factors +/- symptoms was 48 months (33-63) and median OS of patients with two i-iii) factors was 16 months (8-24).

Forty-one percent of patients required disease directed therapy (JAK inhibitors in 37, stem cell transplantation in 8, respectively). Patients without the need for therapy or those who received JAK inhibitor had superior median OS (range 81-100 months) over treated patients without exposure to JAK inhibitors (median OS of 45 months).

CONCLUSIONS: About 20% of patients with pre-PMF have poor outcome with median OS < 3 years. The use of JAK inhibitor improves outcomes of symptomatic patients in a need for therapy.

Introduction

The 2016 WHO classification of myelofibrosis includes prefibrotic primary myelofibrosis (pre-PMF; fibrosis grading 0-1) and overt PMF (fibrosis grade ≥2).

Pre-PMF has favorable survival when compared to overt PMF, however, pre-PMF patients with intermediate -2 or high risks IPSS still have poor outcome[1].

Objective

We aimed to characterize pre-PMF patients referred to our institution between the years of 2000-2020.

We specifically investigated the role of known IPSS[2] prognostic factors on outcome separated into i) clinical factors (CF): presence of either hemoglobin [hgb] < 10 g/dL / white cells [WBC] > 25 x109/L] or peripheral blasts [bl] ≥1%]; ii) age > 65 years and iii) systemic symptoms.

Materials & Methods

Retrospective chart review of 130 patients with newly diagnosed pre-PMF (median 1.5 months from diagnosis to presentation) who presented to our institution between January 2000 and February 2020.

Only patients with available bone marrow fibrosis grading (EU [3]) were included. Patients were annotated by the presence vs absence of clinical factors (CF): anemia [hgb < 10 g/L], leukocytosis [WBC > 25 x109/L], peripheral blasts [≥1%]; age > 65 years; systemic symptoms into separate groups and their outcome was compared.

Demographics were expressed by descriptive statistics. Overall survival was estimated from the time of presentation using Kaplan Meier method with log rank test.

Results

Tables 1-3 are showing clinical characteristics of 130 patients and OS stratified by age, IPSS and number of CF.

Figures 1-3 outline OS per IPSS [Fig. 1], number of CF/age/symptoms [Fig.2], and therapy received [Fig. 3].

Median OS of the entire cohort was 68 months (95% CI 42-94) with 54% of patients being alive at 5 years. Median follow-up was 43 months (95% CI 28-59).

Acute leukemia occurred in 7 patients (5%) with a median time to development of 40 months (95% CI, 9-178).

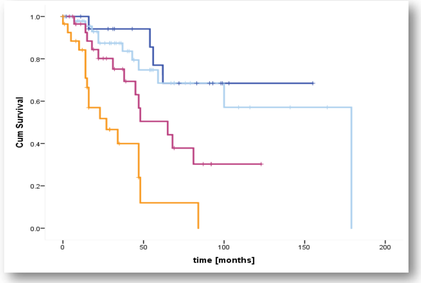
Results - cont.

Table 1. Demographics	N (%)
Fibrosis degree: Gr 0 - 0/1 - 1	9 (7) / 7 (5) / 114 (88)
WBC > 25 x10⁹/L	15 (12)
HGB < 10 g/dL	19 (15)
PLT < 100 x10⁹/L	23 (18)
Constitutional symptoms	84 (65)
PB blasts 1% or more	31 (24)
Karyotype unfavorable*	5 (4)
JAK2/MPL/CALR (tested 116)	74 (64) / 4 (3) / 10 (9)
ASXL1, IDH1/2, EZH2, U2AF1	12 (10)

Table 2. Demographics cont.	N (%)
IPSS low	22 (17)
intermediate 1	50 (38)
intermediate 2	30 (23)
high	28 (22)
Absence of CF	35 (27)
Symptoms only	49 (38)
One CF without symptoms	9 (7)
One CF with symptoms	22 (17)
Two CF +/- symptoms	15 (11)

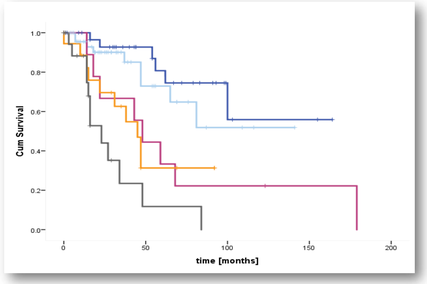
Table 3.	Groups ~ Variables [N. of pt]	Med OS, mos (95% CI)
Age < 65 years	No CF [N 22]	Not reached
	Symptoms only [31]	Not reached
	1 CF [6]	34 (17-52)
	1 CF & symptoms [9]	38 (19-57)
	2 CF & +/- symptoms [1]	15 (NA)
Age > 65 years	No CF [13]	100 (NE)
	Symptoms only [18]	65 (28-102)
	1 CF [3]	58 (36-100)
	1 CF & symptoms [13]	47 (12-82)
	2 CF & +/- symptoms [14]	16 (7-25)
IPSS intermediate 1 [1 point]	Age < 65y & symptoms [N 31]	Not reached
	Age < 65y & one CF [N 6]	32 (5-52)
	Age > 65y only [N 13]	100 (NE)
IPSS intermediate 2 [2 points]	Age < 65y & one CF & symptoms [N 9]	42 (19-54)
	Age < 65y & symptoms [N 18]	65 (28-101)
	Age > 65y & one CF [N 13]	60 (36-100)
IPSS intermediate 3 [3+ points]	Age < 65y & symptoms & two CF [N 1]	15 (NA)
	Age > 65y & one CF & symptoms [N 13]	47 (13-81)
	Age > 65y & two CF +/- symptoms [N 14]	16 (7-25)

Figure 1. OS ~ IPSS



IPSS, N/events	Med OS, mos (95% CI)
low, 22/4	Not reached
Int -1, 50/11	179 (65-NE)
Int-2, 30/13	65 (32-98)
High, 27/11	27 (5-49)

Figure 2. OS ~ presence of risk factors

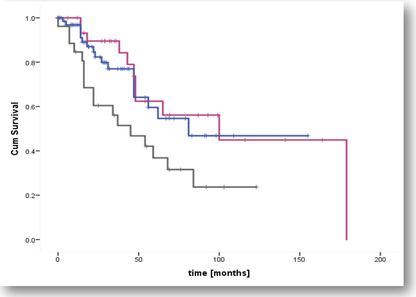


Factors, N/events	Med OS, mos (95% CI)
None (< 65y), 35/6	Not reached
Symptoms (+/- 65y), 49/9	Not reached
1 CF (-) Symptoms, 9/8	48 (33-63)
1 CF (+) Symptoms, 18/10	45 (32-58)
2 CF (+/-) Symptoms, 19/12	23 (14-32)

Results - cont.

Therapy during follow-up = 53 (41%): JAK inhibitors in 31, stem cell transplantation in 8.

Figure 3. OS ~ therapy with / without JAKi vs untreated patients



Group, N/events	Med OS, months (95% CI)
Treated without JAKi, 26/17	45 (16-74)
Treated with JAKi, 31/11	100 (17-183)
Untreated, 73/17	81 (65 – NE)

Patients who needed therapy and were exposed to JAK inhibitors had superior outcome to patients without it.

Moreover, their outcome was comparable to patient who did not require treatment during their observation time.

Summary

Presence of more adverse clinical factors is the strongest predictor of unfavorable outcome of patients with pre-PMF.

Up to 20% of patients might represent high risk category with inferior OS < 3 years and the classification of Pre-PMF, respectively absence of fibrosis at diagnosis, shall not determine their therapeutic approach.

Up to 40% of patients required therapy during their observation and the use of JAK inhibitors might have significantly improved the outcome of these patients.

References

[1]Guglielmelli et al. Blood. 2017;129(24):3227–3236.
[2]Cervantes, et al. Blood. 2009;113(13):2895–901.
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