Leukemia Research 59 (2017) 110–116

Contents lists available at ScienceDirect

Leukemia Research

journal homepage: www.elsevier.com/locate/leukres

Research paper

Patients with post-essential thrombocythemia and post-polycythemia vera differ from patients with primary myelofibrosis

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ARTICLE INFO

Keywords:
Post
essential thrombocythemia myelofibrosis
Post
polycythemia vera myelofibrosis
Primary myelofibrosis
Prognosis

ABSTRACT

Prognostic scoring systems for primary myelofibrosis (PMF) are not accurate in patients with post-essential thrombocythemia and post-polycythemia vera myelofibrosis (PET-MF; PPV-MF). Given the paucity of data describing the clinical characteristics, disease course and outcomes of these patients, we sought to describe and compare the clinical characteristics and outcomes of 755 patients with PMF, 181 with PPV-MF, and 163 with PET-MF referred to our institution between 1984 and 2013. The median follow-up was 31 months, and 56% (n = 616) patients had died. Over an observation period of 3502 person-years, 11% of patients had progression to AML, with similar rates among groups. The proportion of patients with transfusion dependency (higher in PMF), leukocytosis and systemic symptoms (higher in PPV-MF), and thrombocytopenia (higher in PMF, PPV-MF) differed among groups. Median overall survival (OS) was longest in PET-MF patients (73 mo vs 45 mo (PMF) vs 48 mo (PPV-MF), $p < 0.001$). Stratification of OS by DIPSS was only discriminatory in patients with PMF, and it failed to distinguish higher risk patients with PPV/PET-MF. In multivariate analysis, predictors of inferior OS were higher age, anemia, systemic symptoms, thrombocytopenia, and high peripheral blasts in PMF; age, anemia, and systemic symptoms for PPV-MF; and anemia, peripheral blasts and thrombocytopenia in PET-MF. Although the clinical characteristics of PPV/PET-MF patients are not substantially different from those with PMF, their outcomes differ and prognostic scoring systems for PET/PPV-MF should be improved.

1. Introduction

The classical Ph negative chronic myeloproliferative neoplasms (MPN) polycythemia vera (PV) and essential thrombocythemia (ET), though considered relatively benign, share a propensity to progress toward a fibrotic stage (so-called post polycythemia vera myelofibrosis, [PPV-MF] and post essential thrombocythemia myelofibrosis [PET-MF]). PPV- and PET-MF, like primary MF (PMF), are characterized by typical MF features: decreased peripheral blood counts owing to accumulation of reticulin/collagen fibrosis and subsequent bone marrow failure; extramedullary hematopoiesis often accompanied by significant splenomegaly; and debilitating systemic symptoms [1]. PPV-MF and PET-MF are therefore considered to be a natural evolution of these neoplasms, with median time to transformation of 7–20 years from PV/ET diagnosis [2–6]. The cumulative incidence of PPV-MF and PET-MF at 15 years has been reported to be between 5 and 14% for PV and 1.6-9% for ET [2,7–9]. Although multiple factors have been reported to influence the rate of transformation, leukocytosis $> 15 \times 10^9$ is the most consistently reported factor [10]. Histopathologic findings in the bone marrow of PET/PPV-MF and PMF patients share overlapping features, and clinical characteristics are also very similar, with a typical picture of bone marrow failure, splenomegaly and chronic inflammatory status, leading to worsening quality of life and cachexia.

Few studies have specifically focused on comparing biologic, clinical and prognostic features of PET/PPV-MF patients [11–13] with those of patients with PMF and findings have been conflicting [13–18].

Prognostication in PPV-MF and PET-MF is evolving, and evidence suggests that the International Prognostic Score System (IPSS), an established prognostication tool in PMF, can't accurately discriminate different risk categories in PET/PPV-MF patients. However, there is a paucity of data describing clinical characteristics, disease course and outcomes of patients with PET/PPV-MF. In clinical practice, PET/PPV-MF patients are managed similarly to those with PMF; however, whether this practice should change is not known. Here, we describe the clinicopathologic characteristics of patients with PET/PPV-MF and compare their clinical, biologic, and prognostic features with those of PMF patients seen at our center.

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http://dx.doi.org/10.1016/j.leukres.2017.06.001
Received 30 March 2017; Received in revised form 30 May 2017; Accepted 1 June 2017
Available online 02 June 2017
0145-2126/

2. Patients and methods

We retrospectively reviewed the medical records of 1099 patients with MF who were referred to our institution between 1984 and 2013. PMF was diagnosed according to 2008 World Health Organization (WHO) criteria. PET/PPV-MF was diagnosed according to The International Working Group for Myelofibrosis Research and Treatment (IWG-MRT) criteria, which requires a previously documented World Health Organization (WHO)-defined diagnosis of PV or ET and the presence of bone marrow fibrosis grade ≥ 2 (3-point scale) or ≥3 (4-point scale) and two or more additional features: anemia (≥ 2 mg/l decrease from baseline), a leukoerythroblastic peripheral blood smear, splenomegaly, or ≥1 constitutional symptoms, sustained loss of need for phlebotomy and/or cytoreductive therapy for PV or elevated lactate dehydrogenase for ET [19]. Diagnoses of PV or ET were established based on WHO criteria in use at the time of diagnosis. Bone marrow fibrosis grading was assessed according to European Consensus criteria [20]. Molecular testing was performed by real time PCR-based sequencing, using a next generation sequencing platform in our CLIA-certified molecular diagnostic laboratory, as previously reported [21]. All clinical data were collected at the time of referral. Overall survival (OS) was calculated from the date of referral to the date of last follow-up or death, whichever came first. Clinicopathological parameters (categorical and continuous variables) were analyzed by the Fisher's exact, Kruskal–Wallis or Mann–Whitney *U* tests, as appropriate. Survival analyses were carried out with the Kaplan–Meier method and compared with the log-rank test. Patients were not censored at the time of SCT (n = 99) for the purpose of OS analysis, due to the retrospective study design and because we were not evaluating the impact of therapy. Associations between the clinicopathological factors and survival were assessed by univariate and multivariate analysis. Variables with statistical significance on univariate tests were subsequently analyzed in a multivariate model by using Cox proportional hazard regression with stepwise forward selection. All *p*-values are two-sided and $p < 0.05$ was considered to be statistically significant. All statistical computations were performed using SPSS, version 23.0 (Chicago, IL).

3. Results

3.1. Demographics and clinic-pathological characteristics

A total of 1099 patients (755 PMF, 181 PPV-MF, 163 PET-MF) were included in our study (Table 1). Median time to presentation from MF diagnosis was significantly longer in patients with PMF than in those with PPV-MF and PET-MF (4 vs 1 vs 2 months, $p < 0.001$). Of 1099 patients, 595 (375 PMF, 122 PPV-MF, and 98 PET-MF) presented to our institution within 3 months from MF diagnosis and were previously untreated. Among patients who presented to our institution more than 3 months from diagnosis, the median time to presentation was 21 months (range, 4–382) for PMF (n = 380), 17.5 (range, 4–174) for PPV-MF (n = 59), and 21 months (range, 4–149) for PET-MF (n = 65) (*p*-value = 0.07).

Sixty-one percent of patients were men (n = 668), with a significantly higher proportion (65%) among patients with PMF ($p < 0.003$). The median age at MF diagnosis was 65 years (range, 20–89) and was similar in all groups. Patients with PMF were more frequently transfusion dependent; those with PPV-MF had higher leukocytosis (WBC > 25 x 109/L) and systemic symptoms with significant splenomegaly; and those with PET-MF were less likely to be thrombocytopenic (platelets < 100 x 109/L) (Table 1). Other clinical features did not differ among subtypes.

Cytogenetic data with ≥ 10 analyzable metaphases were obtained in 981 (89%) patients, 660 with PMF and 321 with PET/PPV-MF. Overall, 360 (37%) patients had an abnormal karyotype (Abn), and 17% of them had 3 or more abnormalities (complex karyotype, CK, n = 62). Abnormal karyotypes present in > 10% of patients were single 20q- (n = 75, 21%), single 13q- (n = 38, 11%), and CK (n = 62, 17%). Other abnormalities, such as single +8, +9, single −7/7q-, −5/5q-, or various combinations of two Abn occurred less frequently. Importantly, chromosome (chr) 17 Abn were found only in patients with PMF, while all other Abn were similarly distributed among PMF and PET/PPV-MF (Table 2).

In total, 698 patients (69%) were tested for all 3 known driver mutations (JAK2 V617F, MPL and CALR). An additional 170 patients (39 PET-MF, 131 PMF) who tested negative for JAK2 and MPL, were not tested for CALR mutations. The distribution of driver mutations was similar among disease subtypes (Table 2). As expected, the majority of patients were JAK2 positive (n = 592; 68%) and all PPV-MF patients

Table 1
Demographics and clinical characteristics of all patients.

Characteristics	PMF (N = 755)	PPV-MF (N = 181)	PET-MF (N = 163)
Median age, years (range)	65 (20–88)	67 (32–89)	65 (27–87)
Age > 65 years, N (%)	362 (48)	102 (56)	81 (50)
Males, N (%)	488 (65)*	104 (57.5)	76 (47)
Median WBC, 10^9/L (range)	9.5 (0−361)	**14 (1–191)***	8 (2–61)
WBC > 25 × 10^9/L, N (%)	133 (18)	**53 (29)***	16 (10)
Median platelets, 10^9/L (range)	188 (1–1364)	213 (6–1958)	304 (14–2690)
Platelets < 100 × 10^9/L, N (%)	218 (29)	44 (24)	**14 (9)***
Median hemoglobin, g/dL (range)	10 (5–19)	11 (5–18)	10.5 (4–17)
Hgb < 10 g/dL, N (%)	321 (43)	68 (38)	67 (41)
Peripheral blasts ≥ 1%, N (%)	368 (49)	80 (44)	73 (45)
Splenomegaly, N/known (%)	416/752 (55)	**143/179 (80)***	65/163 (40)
Symptoms, N (%)	531 (70)	**146 (81)***	108 (66)
Transfusion dependency, N (%)	**217 (29)***	30 (17)	33 (20)

*statistically significant differences ($p < 0.05$) in bold.

Table 2
Clinical characteristics of all patients, molecular data and karyotype.

Pt. Characteristics	PMF, N = 755	PET/MF, N = 163	PPV-MF, N = 181
JAK2 positive, N (% of eval.)	369/442 (83)	65/99 (66)	157/157 (100)
Median JAK2 allele frequency, % (range)	47 (1–99)	58 (7–96)	**86 (5–99)***
MPL positive, N (%)	22 (5)	7 (7)	–
CALR positive, N (%)	32 (7)	23 (23)	–
Triple negative, N (%)	21 (5)	4 (4)	–
HMR mutations, N (%)	45/198 (22)	7/38 (18)	15/147 (10)
DIPSS − low, N (%)	67 (9)	9 (6)	16 (9)
Int-1, N (%)	261 (35)	68 (42)	69 (38)
Int-2, N (%)	325 (43)	80 (49)	55 (31)
High, N (%)	96 (13)	23 (14)	23 (13)
Advanced BM fibrosis, N (%)	588/667 (88)	150/162 (93)	**145/149 (97)***
Karyotype, total eval., N	N = 660	N = 113	N = 208
Diploid, N (%/)	429 (65)	56 (50)	136 (65)
Single Abn, N (%)	144 (22)	44 (39)	31 (15)
Single Deletion 13q/20q, N	75	17	21
Deletion 7/7q, 5/5q, 12p-, INV (3), Abn 17, N	18	3	2
All Others**, N	51	24	8
Double Abn, N (%)	54 (8)	5 (4)	20 (10)
Including Abn 5, 7, 12p, 11q23, 17, N	16	–	3
Including Abn 13q, 20q, N	10	3	2
All Others**, N	28	2	15
Complex (≥3 Abn), N (%)	33 (5)	8 (7)	21 (10)

*Statistically significant differences ($p < 0.05$) are shown in bold; Advanced bone marrow fibrosis = Grade 2 or higher according to European grading; HMR mutations = ASXL1, IDH1, IDH2, EZH2; ** Ab = single or combinations of: INV, DER and TRANSL. of 1, 3, 6, 8, 9, 12, 13, 15, 18 and Y; trisomy of 1, 8, 9, 21, 13; ADD of 21, 2; DEL 6p, 8p, 1p, 13q, 20q, Y; 131 patients with PMF and 39 patients with PET-MF who were negative for JAK2 and MPL, but not tested for CALR are not included in the table.