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Patients with Polycythemia Vera and Essential Thrombocythemia with Prior Malignancy Do Not Have Significantly Worse Outcome

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Abstract

The clinical relevance of prior malignancy (PM) in patients with essential thrombocythemia (ET) and polycythemia vera (PV) is largely unknown. We retrospectively evaluated 437 patients (ET, n=263; PV, n=174) treated at MD Anderson between 1960 and 2010. Forty-four patients had PM (ET, 10%; PV, 11%), with median time to diagnosis of 66 months. PM was not associated with abnormal cytogenetics, JAK2-mutation frequency, blood-cell counts or progression to acute leukemia or myelofibrosis. In multivariate analysis, only older age and high LDH levels were associated with worse OS. In conclusion, PM does not predict worse outcomes for patients with ET and PV.

Keywords

myeloproliferative disorders; polycythemia vera; essential thrombocythemia; prior malignancy; transformation to acute leukemia; transformation to myelofibrosis

Introduction

Essential thrombocythemia (ET) and polycythemia vera (PV) are chronic myeloproliferative neoplasms (MPNs) characterized primarily by autonomous production of platelets and increases in red blood cell mass, respectively. Patients with these disorders are often

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Authors' Contributions

MC, MCT, HP, SP and LZ helped in collecting the data; MCT, HP, SP and LZ performed the statistical analysis; SV, HK and JC reviewed and edited the manuscript; and MC, SV wrote the manuscript.

Conflict of Interest

All authors have no conflict of interest to report.

asymptomatic and the diagnosis is made incidentally when a routine complete blood count shows thrombocytosis or erythrocytosis. The median age at diagnosis for ET and PV is 60 years, [1] but they can occur at any age.[2, 3] Although the overall outcome of patients with these disorders is very good, with survival times exceeding several decades in some patients [4], in the most recent World Health Organization (WHO) classification,[5] the nomenclature was changed from “myeloproliferative disorders” to “myeloproliferative neoplasms” to stress the importance of the clonality of these disorders and their potential to transform to myelofibrosis and acute leukemia. This decision was supported in part by the demonstration of JAK2 mutations in almost all patients with PV and about 50% of those with ET.[6] Patients with ET and PV are at increased risk of thromboembolic complications, leading to significant morbidity often necessitating the use of aspirin and cytoreductive agents.[7, 8] It has been very well established that patients with MPN have increased risk of developing secondary cancer. Radaelli et al retrospectively investigated long-term development of hematological and non-hematological second malignancies in 331 patients with ET, analyzing possible associations with chemotherapy treatments. Median follow-up was 108 months. After a median time of 87 months from the diagnosis of ET, 43 patients developed a second malignancy, hematological in 15 and non-hematological in 28, for an overall cumulative incidence of 13%. According to the type of treatment, second malignancies were documented in 11.2% of patients treated with only hydroxyurea (HU), in 26.3% of patients who received only Alkylating agents (ALK), and in 25% of those treated with ALK followed by HU. Ten cases (7.3%) were recorded among those who did not receive any treatment.[9] Others also investigated the risk of second malignancy after the diagnosis of ET and PV and found similar results. [10-12] The clinical relevance of a diagnosed PM in patients with PV or ET is largely unknown. This led us to investigate whether PM in patients with PV and ET was associated with specific demographic or clinical characteristics and its effects on outcome of these patients.

Patients and Methods

The MPN database at MD Anderson Cancer Center was queried for patients with ET and PV who presented to our institution from January 1960 to September 2010. Institutional review board approval was obtained for the conduct of this study. We collected relevant clinical and laboratory data by reviewing the patients’ medical records. Diagnosis of ET or PV was reconfirmed according to the WHO criteria.[5] In addition, we recorded whether a pathologically confirmed PM was present in these patients, its histology, and treatment received. Statistical analyses were performed to assess whether there were significant differences in characteristics or outcomes between patients with and without a diagnosed PM.

Study variables were summarized using standard descriptive statistics and measures of central tendency, including medians, ranges, frequencies, and percentages. Differences by PM status according to demographic and clinical characteristics were evaluated using the Chi-square or Fisher’s exact tests for discrete variables and the Mann-Whitney *U* test for continuous variables. For time-to-event analyses, we used the Kaplan-Meier method. In a second step, we evaluated factors associated with overall survival using Kaplan-Meier analyses and determined differences using the log rank test. To understand the weighted effect of potential predictors of survival, we constructed a Cox proportional hazard regression model, including as covariates factors with a p-value <0.20 in the univariate analysis. Because transformation to hematological malignancy occurred years after the diagnosis of ET or PV, this variable was handled as a time-dependent variable. A p-value of <.05 (two-tailed) was considered statistically significant. We used PASW Statistics 17.0.2 for Windows (SPSS Inc., Chicago, Illinois).

Results

A total of 437 patients with a diagnosis of ET (n=263) or PV (n=174) were identified and included in our analysis. The median follow up was 97 months (95% CI 86 – 107). Forty four patients were found to have a malignancy prior to the diagnosis of ET or PV: 25 patients (10%) with ET and 19 patients (11%) with PV (Table 1). The median lag time from diagnosis of first malignancy prior to diagnosis of ET or PV was 66 months (range, 4-540 months). The majority of patients had solid tumors (98%), but one patient had been previously diagnosed with classical Hodgkin's lymphoma. This patient was diagnosed with Hodgkin's lymphoma as a child and developed PV close to 33 years later. Three patients (two with ET and one with PV) had more than one PM diagnosed. Skin cancers and melanomas were the most frequent PM (41% of patients) followed by prostate cancers (18%), gynecologic malignancies (14%), and breast cancers (9%). Patients with a PM were treated with surgery (32 patients), chemotherapy (4 patients), radiation (3 patients) or a combination of treatment modalities (6 patients). Only four patients were diagnosed with metastatic or recurrent disease, and in two of these patients, the metastasis occurred after the diagnosis of MPN.

To determine whether certain demographic or clinical characteristics were more common in patients with PM than in those without PM, we measured differences in demographic and clinical characteristics at the time of initial visit to MD Anderson (Table 2). The median age at diagnosis of MPN was higher in patients with a PM than in those without PM. When looking at differences in age by diagnosis (ET or PV) and PM status we found a similar trend. The median age of patients diagnosed with ET was 58 years for those with a PM vs. 47 years for those without ($p = 0.001$). In the PV group, the median age at diagnosis was 67 for those with a PM vs. 50 years for those without ($p = 0.001$). No differences were found in the frequency of JAK2 mutation and blood counts at diagnosis between the 2 groups (Table 2). Cytogenetic abnormalities were not significantly more common in patients with PM than in those without it. However, deletion of the long arm of chromosome 20 was appeared to be more frequent in patients with PM (2/6) than in patients without PM (3/28). Interestingly, chromosome 9 abnormalities (trisomies, inversions and deletions) were the most common chromosomal abnormalities seen in patients without PM (10/28), and none of the patients with PM had chromosomal 9 abnormalities (Supplementary Table 1).

Overall progression to acute leukemia or myelofibrosis was not significantly more common in patients with a PM ($p = 0.12$). Seven patients (2%) without PM developed acute leukemias compared with only 1 patient (2%) who had a PM ($p=0.58$). When we compared PM status by transformation into acute myeloid leukemia, we found no difference (2% of patients with PM vs. 1% of those without; $p = 0.48$). When the patients were classified by transformation to myelofibrosis, we found that a higher proportion of patients with myelofibrosis had a PM than those without (9% vs. 3%) but the difference was not significant ($p = 0.07$). Patients with PM had a marginally shorter time to transformation to acute leukemia or myelofibrosis than those without PM (33 vs. 107 months; $p = 0.05$).

The median overall survival (OS) was significantly shorter in patients with a PM (182 vs. 322 months; $p = 0.001$). When looking at the subgroups by MPN diagnosis and comparing survival by PM status, we observed the OS of patients with ET was 268 months for those with PM vs. 336 months for those without ($p = 0.11$); for patients with PV, the OS was 119 months for those with PM vs. 256 months for those without ($p = 0.001$). To determine which demographic and clinical factors were associated with OS, we assessed the association of age, gender, prior malignancy, use of hydroxyurea, anagrelide or interferon, splenomegaly, splenectomy, performance status, hemoglobin level, WBC, platelet count, creatinine level (1.3 vs. >1.3), serum LDH level (abnormal high to normal value), JAK2 mutation and

karyotype with OS in a univariate analysis (Table 3). Factors significantly associated with OS included age, gender, prior malignancy, WBC, LDH levels, and karyotype.

To identify independent predictors of OS, we constructed a Cox proportional hazard regression model (Table 4). The covariates included were PM status, age, sex, hydroxyurea treatment, splenomegaly, WBC, LDH and karyotype. Diagnosis of ET or PV and progression to hematological malignancy were also included in the model. Because of the small number of patients for whom JAK2 mutation status was available, we analyzed this group separately and constructed a second model with the covariates already mentioned. In the first model, the independent predictors of OS were age ($p = 0.001$) and LDH level ($p = 0.03$). We observed that older patients had a survival disadvantage, with an increase of 9% in the HR per year of age. Higher levels of LDH at the time of diagnosis were also associated with shorter OS: a one unit increase in LDH or creatinine levels at diagnosis represented a 1% increase in the HR. We did not find interactions between any of the covariates in the model. We observed similar results in the second model that included only the subgroup of patients who had been tested for the JAK2 mutation (data not shown).

Discussion

Recently, Fallah et al [9] reported a higher frequency of PM in patients with PV after analyzing 3,530 patients with PV registered in the Swedish Family Cancer Database, which contains more than 11 million individuals born after 1932. The researchers found that 270 (7%) patients who were diagnosed with cancer before being diagnosed with PV had a significantly higher frequency of thyroid, parathyroid, melanoma and skin cancers than the general population [10]. The authors concluded that patients with these cancer types should be tested for JAK2 mutations when a minimal suspicion of PV is present. Such a recommendation cannot be uniformly adopted and prospective studies should be conducted for further confirmation. However, the authors did not comment on whether PM had an impact on the clinical course of PV or survival of these patients. To the best of our knowledge, our study is the first large retrospective hospital-based study evaluating the impact of PM on the outcome of patients with a diagnosis of PV or ET. Our study showed that 11% of patients with PV and 10% of patients with ET had a PM, which is consistent with the report from Fallah et al. Skin cancers, prostate cancer and breast cancer were the most frequent PM found in our study. This is not surprising because these cancers are the most common cancers encountered in the general population.[13]

The pathophysiologic impact of PM on the development of ET or PV is not well understood. Whether the presence of malignancy induces some biochemical changes leading to the development of these disorders is not well known. While chemotherapy and radiation therapy are well known to increase the risk of leukemia and second cancers, the effect of these therapeutic modalities on the development and survival of patients with ET or PV cannot be accurately assessed because most of these patients were originally treated elsewhere and details of prior treatment regimens are not available.

In this study, we found that LDH level was an independent predictor of survival. Previous studies have shown that increased LDH is associated with increased bone marrow proliferation and increased risk of progression to myelofibrosis.[14-16] In one study, investigators compared the LDH levels in patients with secondary polycythemia with those with PV, ET or MF and found that the mean LDH level was moderately increased in patients with PV and ET and markedly increased in patients with MF when compared with patients with secondary polycythemia.[15] Our finding of an association between LDH level and survival indicates that serum LDH level may be associated with prognosis in patients with MPN. However, further evaluation of this association in larger prospective studies is needed

to determine whether incorporating LDH levels in monitoring and treatment strategies is warranted.

The major limitations of our study are related to the fact that this is a retrospective, chart review study and our sample arises from a single institution. Nevertheless, our results suggest that PM in patients with ET and PV does not have clinical relevance for the outcome of these patients.

Conclusion

This current study, to the best of our knowledge, is the first longitudinal retrospective study analyzing the impact of PM on the development of PV or ET. Patients with PM were diagnosed with PV or ET at a later age, with a median lag time to diagnosis of approximately 5 years. However, after adjusting for age in the multivariate analysis, PM was not associated with shorter OS. Thus, patients with PM are diagnosed with PV or ET at an older age but are not likely to have worse outcome when compared to patients without PM. These findings should be further assessed and confirmed by other groups and be studied on a larger scale in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Distribution of Prior Malignancies by Cancer Subtype

Cancer Subtype	ET (n=25)	PV (n=19)
Basal cell carcinoma	4	4
Bladder cancer	1	1
Breast cancer	3	1
Cervical cancer	2	1
Colon cancer	1	2
Hodgkin's lymphoma	0	1
Lung cancer	0	1
Papillary Teratoma	0	1
Prostate cancer	5	3
Sarcoma	1	1
Squamous cell carcinoma (head & neck)	4	0
Squamous cell carcinoma (skin)	0	2
Squamous cell carcinoma (vulva)	1	0
Thyroid cancer	2	1
Uterine cancer	1	0
Melanoma	3	1
Total no. cancers	28	20

Table 2

Univariate Analysis of Demographics and Clinical Characteristics of All Patients (N=437)

		Patients without prior malignancy (n=393)	Patients with prior malignancy (n=44)	P-value ^a
Age, median (range)		48 (15-84)	61 (20-80)	0.001
Sex, n (%)	Male	153 (39)	20 (46)	0.41
	Female	240 (61)	24 (54)	
Hgb, median (range)		13.7 (7.1-23.5)	13.4 (9.1-17.7)	0.59
WBC, median (range)		9 (1.9-161.9)	9.4 (3.4-148.0)	0.15
Platelets, median (range)		586 (12-6512)	533 (23-1581)	0.37
Creatinine, median (range)		0.9 (0.2-4.8)	0.9 (0.6-3.7)	0.48
Billirubin, median (range)		0.5 (0.1-3.3)	0.6 (0.2-4.9)	0.26
LDH, median (range)		565 (161-4371)	616 (362-2216)	0.03
Jak2 V617F+, n (%)		140 of 191 tested	18 of 23 tested	0.69 ^b
No. Jak2 V617F alleles, median (range)		34 (2.4-100)	71 (5.9-98.1)	0.03
Splenomegaly, n(%)	Yes	58 (15)	8 (19)	.56 ^b
	No	324 (85)	35 (81)	
	Splenectomy	11 (3)	1 (2)	.99 ^b
Performance Status, n(%)	0	298 (76)	33 (75)	0.820
	1	91 (23)	11 (23)	
	2	3 (1)	0 (0)	
Cytogenetics, n(%)	Diploid	312 (92)	36 (86)	0.19
	Abnormal	28 (8)	6 (14)	
Prior treatment, n(%)	HU	227 (58)	32 (73)	0.05
	Anagrelide	129 (33)	16 (36)	0.64
	IFN	64 (16)	5 (11)	0.40
Transformation, n (%)	MFIB	12 (3)	4 (9)	0.12
	AML+Acute Biphentotypic+Acute LymphoblasticLeuk	5+1+1(2)	1 (2)	
	No	374 (95)	40 (89)	

Abbreviations: Hgb, hemoglobin; WBC, white blood cell count; LDH, lactate dehydrogenase; NA, not applicable.

^aP-value < .05 is considered significant.^bFisher's exact test.

Table 3

Univariate Analysis of Clinical and Demographic Characteristics and their Association with Overall Survival

		Median Survival (mos)	95% CI	P-value
Age	<=65 years	322	236.3-408.5	0.001
	>65 years	102	86.3-118.5	
Sex	Men	249	166.1-330.9	0.02
	Women	268	231.8-303.8	
Prior Malignancy	No	322	256.8-388.0	0.001
	Yes	182	86.1-278.8	
Hydroxyurea	No	249	218.8-278.3	0.11
	Yes	324	231.6-416.6	
Anagrelide	No	292	229.9-354.3	0.47
	Yes	256	207.3-304.5	
Interferon	No	264	225.9-301.1	0.32
	Yes	336	177.0-494.6	
Splenomegaly	No	264	243.5-283.5	0.12
	Yes	227	160.5-293.5	
Splenectomy	No	264	225.6-301.4	0.11
	Yes	NR		
PS	0	292	235.0-349.2	0.33
	1	256	207.2-304.6	
	2	NR	NR	
WBC	<=9000	322	209.8-435.1	0.005
	>9000	249	207.4-289.6	
HGB	=>10.0	292	233.6-350.6	0.65
	8.0 – 9.9	268	NR	
	<8.0	322	NR	
Platelets	<50	98	0.0-197.7	0.91
	=>50	268	227.8-307.8	
Creatinine	<=1.3	268	225.6-309.9	0.35
	>1.3	NR		
LDH^a	>600	264	209.4-317.6	0.01
	<=600	324	207.6-440.6	
JAK2 mutation^b	>36	324	168.5-479.7	0.05
	0-36	NR	NR	
Karyotype	Diploid	292	245.3-338.9	0.04
	Abnormal	175	98.2-250.8	

Abbreviations: NR, not reached; CI, confidence interval; PS, performance status; WBC, white blood cell count; HGB, hemoglobin level; LDH, lactate dehydrogenase

^aUpper limit of normal (600) was used as a cutpoint for the analysis.

^bMedian JAK2 allele burden was used as a cutpoint for the analysis.

Table 4

Multivariate Analysis of Demographic and Clinical Factors Associated with Overall Survival in Patients with Diagnosis of ET or PV

		P-value	HR	95.0% CI for HR
Diagnosis		0.86		0.517–1.715
	ET		1.000	
	PV		0.942	
Previous malignancy		0.27		0.332–1.354
	Yes		1.000	
	No		0.670	
Sex		0.14		0.381–1.144
	Men		1.000	
	Women		0.660	
Hydroxyurea		0.60		0.653–2.095
	Yes		1.000	
	No		1.169	
Splenomegaly		0.34		0.702–2.823
	No		1.000	
	Yes		1.408	
Abnormal karyotype		0.32		0.692–3.057
	No		1.000	
	Yes		1.455	
WBC		0.56	1.004	0.990–1.018
Age at diagnosis		.001	1.090	1.061–1.119
LDH		0.03	1.001	1.000–1.001
Transformation *		0.25	1.002	0.998–1.006

Abbreviations: HR, hazard ratio; CI, confidence interval; WBC, white blood cell count; LDH, lactate dehydrogenase

* Time-dependent variable.