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SIGNIFICANCE OF CYTOGENETIC ABNORMALITIES IN PATIENTS WITH POLYCYTHEMIA VERA

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Abstract

We analyzed 133 patients with polycythemia vera (PV) that were followed at our institution (median 7.5 years) and had adequate cytogenetic information. The 5-, 10-, and 15-year survival rates were 93%, 79%, and 64%, respectively, with the median projected overall survival of 24 years. Nineteen patients (14%) had abnormal cytogenetics at any time during the disease course (no survival difference). Sixteen patients (12%) transformed during follow up, after a median of 8.5 years, to myelofibrosis (11), acute myeloid leukemia (4), or myelodysplastic syndrome (1); 8 had cytogenetic abnormalities. Among 133 patients, 39 were newly diagnosed: 33 with normal and 6 with abnormal cytogenetics (no survival difference); 9 transformed (6 with normal and 3 with abnormal cytogenetics at diagnosis). In keeping with other smaller series, the presence of chromosomal abnormalities may have a role in the transformation of patients with PV; survival was not affected likely due to short follow up.

Keywords

polycythemia vera; cytogenetic abnormality; survival; transformation

Introduction

Polycythemia vera (PV) is a Philadelphia chromosome-negative myeloproliferative neoplasm (MPN) primarily characterized by increased red blood cell production. The World Health Organization (WHO) set forth new diagnostic criteria for PV in 2008 based on laboratory, pathological and molecular findings [1]. Of the latter, the most frequent abnormality detected in patients with PV is the JAK2 V617F mutation, which is present in approximately 97% of patients. JAK2 V617F-negative patients have been found to carry functionally similar somatic mutations mapping to exon 12 of the JAK2 gene [2–6]. In addition to JAK2 mutations, cytogenetic abnormalities can also be detected in approximately 13–35% of patients with PV [7–13]. The most common abnormalities observed in PV are trisomy of chromosomes 8 or 9 and del(20) q. Their role in the pathogenesis of the disease remains undefined as none of them have been conclusively shown to be poor prognostic factor [10]. However, some reports have suggested that patients with PV carrying clones with chromosomal abnormalities at the time of diagnosis have a shorter survival compared to those with a diploid karyotype [8]. As expected, the frequency

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of cytogenetic abnormalities increases significantly when patients with PV transform to acute myeloid leukemia (AML), myelodysplastic syndrome (MDS) or myelofibrosis (MF) [14]. In this retrospective study we analyzed the role of aberrant chromosomal abnormalities on transformation and survival in 133 patients with PV with informative cytogenetic results at presentation to and followed at our institution.

METHODS

The MPN database at MD Anderson Cancer Center was queried for patients with PV who presented at our institution from September 1961 to December 2008, for whom informative cytogenetic result was available. Institutional review board approval was obtained for the conduct of this study. Clinical and histopathological results in identified patients were reviewed and the diagnosis of PV was reconfirmed according to the WHO criteria [1]. Metaphases obtained from unstimulated bone marrow aspirate cultures using standard techniques were used for performing conventional cytogenetic analysis. Results were reported using the International System for Human Cytogenetic Nomenclature. Cytogenetic results were considered pathologic when at least two abnormal metaphases were identified to carry a structural abnormality or a chromosome gain, or when at least three metaphases with the same chromosome loss were identified. If a patient was referred and assessed at our center within four months of initial diagnosis of PV, per standard practice the cytogenetic testing was considered to be ‘at initial diagnosis’. All other testing was considered ‘beyond initial diagnosis’. When possible, JAK2 V617F mutation status was analyzed in stored bone marrow specimens, using previously published assay [15]. Statistical analyses were performed using Prism 5 for Windows software (GraphPad Software, Inc.). Characteristics of the patient groups were compared using the Mann-Whitney and Fisher exact tests. Projected survival curves of patients with and without cytogenetic abnormality were plotted according to the Kaplan–Meier method; the homogeneity of the survival curves for different groups was tested by log-rank test.

RESULTS

We identified 133 patients with PV with adequate metaphases for interpretation of cytogenetic testing at presentation at our institution (Table I). The median number of cytogenetic assessments per patient performed was 1 (range 1–8). However, cytogenetic analysis was performed in two or more occasions in 37 (28%) patients during follow-up. The incidence of cytogenetic abnormalities for the entire cohort was 14% (19 patients; Table II). The most common abnormalities detected involved chromosome 9 (n=3), 12 (n=2) and 20 (n=2), with most other abnormalities being detected only in one occasion.

The 5-, 10-, and 15-year survival rates for the cohort of 133 patients from the time of diagnosis were 93%, 79%, and 64%, respectively. The median overall survival for the whole cohort was 24 years. We did not observed significant differences regarding overall survival between the 19 patients with PV carrying cytogenetic abnormalities at any time during the disease course and those 114 patients without chromosomal abnormalities (p=0.12). Of the 133 patients, 16 (12%) transformed during follow up: 11 transformed to MF, 4 to AML, and 1 to MDS. Of the 16, 8 had cytogenetic abnormalities (Table II). The overall annual rate of transformation (to MF, AML, or MDS) was 2.7%. The median time from diagnosis to transformation for the 16 patients was 8.5 years (range 0.3–21.5). $JAK2^{V617F}$ mutation status was available in 88 (66%) patients. We found no association between the presence of the mutation in the JAK2 gene, karyotypic abnormalities, and survival. The $JAK2^{V617F}$ mutation was detected in 11 of 11 (100%) patients with an abnormal karyotype and in 71 of 77 (92%) patients with a normal karyotype at presentation.

Of the 133 patients 39 were considered to be newly diagnosed and 6 (15%) of them had abnormal cytogenetics (first 6 patients in Table II). Interestingly, of the 6 newly diagnosed patients that had abnormal cytogenetics, 2 exhibited cytogenetic changes with respect to baseline during subsequent cytogenetic follow-up assessments (patients 5 and 6 in Table II). Those changes included becoming diploid in one case (of note, patient was treated with interferon) and the detection of new clones carrying additional cytogenetic abnormalities in the other case (this patient later transformed to MF). Three of the 33 newly diagnosed patients with normal cytogenetics subsequently developed cytogenetic abnormalities during follow-up (patients 14, 15, and 16 in Table II); two of them had abnormal cytogenetics at the time of transformation, while one did not transform during follow up. Overall among the 39 newly diagnosed patients, 9 transformed to AML, MDS, or MF, including 6 of 33 with initial diploid cytogenetics and 3 of 6 with initial abnormal cytogenetics (p=0.09). However, there was no survival difference between newly diagnosed patients with and those without cytogenetic abnormalities (p=0.4).

DISCUSSION

We herein present results on a large cohort of patients with PV (n=133) from a single institution, regarding the impact of cytogenetic abnormalities on long-term outcomes. The rate of cytogenetic abnormalities detected at baseline, as well as overall at any time during the disease course, was 14%, in accord with previous reports [7–13]. However, cytogenetic analysis was performed in two or more occasions in only 28% of patients during follow-up. Performance of more than one cytogenetic testing in a given patient over time was entirely dependent on the management/decision of a treating physician. This potentially introduces a bias in the assessment of the role of cytogenetic abnormalities in the natural history of PV (e.g. patients showing significant change in the blood cell count would have bone marrow biopsy and cytogenetic testing more readily performed to assess for possible progression of the disease). While some older reports have described an incidence of cytogenetic aberrancies as high as 44%, this appears to relate to the widespread use of P32 and/or alkylating agents as therapy for PV at that time [8, 12, 13]. This contention is supported by the lower rate of transformation reported in the present series, in which only one patient experiencing transformation had previously received an alkylating agent (chlorambucil) and none had received P32. The patient who received chlorambucil did not have cytogenetic abnormality during the disease course. In our series, those patients that acquired cytogenetic abnormalities during the disease course were treated with hydroxyurea and one received anagrelide.

The most common cytogenetic abnormalities reported in PV and other MPNs are trisomy of chromosomes 1, 8, and 9, as well as del(13) and del(20) [7, 16]. With the exception of trisomy 8 and del(13), we identified all other common cytogenetic abnormalities in our cohort of patients. Interestingly, one patient carried the t(12;21), which is usually found in childhood B-lineage acute lymphoblastic leukemia, typically conferring a favorable prognosis, but otherwise rarely observed in PV [17].

Our results are consistent with other smaller series reporting that a substantial number of patients with PV who eventually underwent transformation had a normal karyotype [8, 9, 11–13]. In our experience, half (8 of 16) patients that transformed had diploid cytogenetics. Similar findings have been reported for patients with essential thrombocythemia [18]. This difficulty in predicting disease transformation based solely on the presence of cytogenetic abnormalities in patients with PV is in accordance with previous reports by other groups [12, 13, 20, and 21]. Albeit more rarely, cytogenetic abnormalities can also become undetectable during the course of the disease, a phenomenon that was observed in one of our patients

upon therapy with pegylated interferon-alfa-2a. Whether such genetic instability is a part of the natural history of the disease or an effect of specific therapy remains unknown[11, 12].

It is evident that the process of transformation in PV is complex and cytogenetic abnormalities appear to play only a partial role, with yet unidentified factors significantly contributing to the transformation process. One of the factors potentially important for PV transformation to MF is the presence of a high mutant $JAK2^{V617F}$ allele burden [19]. To investigate the role of $JAK2^{V617F}$ allelic burden in MF transformation, we performed allele-specific PCR analysis for $JAK2^{V617F}$ in 88 patients. Similar to other investigators, we found no correlation between $JAK2^{V617F}$ allelic burden and risk of transformation [9].

Some reports have suggested a deleterious impact of chromosomal abnormalities on survival in patients with PV. Diez-Martin et al. analyzed 104 patients with PV [8]. In the subgroup of 24 patients for whom cytogenetic information was available at the time of diagnosis, 4 were found to have an abnormal karyotype and their survival was significantly shorter. Our results in a 39 newly diagnosed patients appear to support the contention that karyotypic abnormalities at diagnosis might be associated with increased risk of transformation but not survival. However, the median follow up of our cohort is relatively short and may have significant influence on the observed rate of transformations and overall survival. Therefore, a longer follow-up on a larger population of PV patients in the context of an international multicenter effort would be required to answer whether cytogenetic abnormalities in PV patients are adverse prognostic factor for survival.

In conclusion, we established in a large cohort of patients with PV that the incidence of chromosomal abnormalities is approximately 14%. In our experience, the presence of cytogenetic abnormalities in patients with PV may have an impact on the risk of transformation to MF, MDS, or AML.

Acknowledgments

Declaration of Interests

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Table I

Overall patient characteristics

Total number of patients	133
Age (median, range)	57 (18–84)
Male (%)	68 (51)
With splenomegaly/total measured (%)	44/129 (34)
WBC ×10^9/L(median, range)	12.9 (1.9–148.0)
Hgb g/dL (median, range)	14.6 (7.6–23.5)
Platelets ×10^9/L (median, range)	428 (14–4860)
JAK2 mutated/total tested (%)	82/88 (93)
Transformed (%)	16 (12)
Follow up (median, range; years)	7.5 (0–34)

Table II

Outcome of patients with cytogenetic abnormalities

Patient	Dx to MDACC, months	Cytogenetics at presentation to MDACC	Subsequent Cytogenetics	Dx to Clonal Evolution, months	Transformed To	Dx to Transformation, months	Dx to LFU, months (years)	Current Status
1	0	(47,XY,C+)-30%;(46,XY)-70%			MFIB	118	144 (12)	Dead
2	0	46,XX,del(7)(q22),del(7)(q22q32),-22,+mar[13]; 43-46,XX,-5,del(7)(q22),del(7)(q22q32),-22,+1-3mar[cp7]					8 (1)	Dead
3	1	46,XY,T(12;21)(Q21;Q21)[5]; 46,XY[15]			MFIB	51	93 (8)	Dead
4	2	47XX,+9[13]; 46XX[7]					47 (4)	Alive
5	3	46XY,+1,DER(1;22)(Q10;Q10)[17]; 46,XY[3]	46,XY[20]				61 (5)	Alive
6	4	46,XY,del(12)(q15q22)[6]; 46,XY[13]	46,XY,del(12)(q15q22)[15]; 46,XY,del(12)(q15q22),del(20)(q13)[2]; 46,XY[3]	34	MFIB	106	121 (10)	Alive
7	40	47,XX,+9[9]; 46XX[11]					69 (6)	Alive
8	52	46,XY,DER(21)T(1;21)(Q12;p13)[7]; 46,XY[13]					81 (7)	Alive
9	114	46,XX,DEL(11)(Q13)[20]			MFIB	115	117 (10)	Dead
10	132	46,XX,DEL(20)(Q11.2Q13.1)[15]; 46,XX[3]					139 (12)	Dead
11	150	46,XY,del(6)(q21q25),add(11)(p11.2)[2]; 46,XY[28]					221 (18)	Alive
12	176	47,XX,+9[17]					204 (17)	Alive
13	287	46XY DEL(20)(Q11.2)[5]; 46,XY[15]					356 (30)	Dead
14	0	46,XY[20]	42,XY,del(2)(p22),-5,del(6)(q21q25),add(7)(p11.1),del(7)(q22),add(11)(p11.1),-13,-16,del(16)(q22q24),add(17)(p11.1),del(18)(q22),del(20)(q11.2q13.1),-22[16]; 38-39,XY,-4,-5,-7,-10,del(16)(q22q24),-17,-18[cp2]; 46,XY[2]	34	AML	33	37 (3)	Dead
15	0	46,XX(20Q-)[1]; 46,XX[21]	46,XX(20q-)[10]; 46,XX[9]	94			292 (24)	Dead
16	1	46,XX[20]	46,XX,dup(1)(q21q32)[20]	308	MFIB	303	324 (27)	Dead
17	57	46,XY[20]	38-45,XY,add(5){q11.2},-7,-15[7],-22[8]+0-2mar[cp18]; 46,XY[2]	107	MDS	104	107 (9)	Dead
18	101	46,XY[20]	46,XY,der(6)t(1;6)(q25;p25)[18]; 46,XY,der(6)t(1;6)(q25;p25) exhibiting random changes[1]; 46,XY,del(7)(q22)[1]	134	AML	114	133 (11)	Alive
19	221	46,XX[20]	46,XX,der(7)t(1;7)(q21;q36)[15]; 46,XX[5]	324			322 (27)	Dead

Dx = diagnosis; LFU = last follow up; AML = acute myeloid leukemia; MDS = myelodysplastic syndrome; MFIB = myelofibrosis