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Increased likelihood of post-polycythemia vera myelofibrosis in Ph-negative MPN patients with chromosome 12 abnormalities

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ABSTRACT

Chromosome 12 (Chr12) abnormalities have been described for individual patients with Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-neg MPN), however the frequency, characteristics, and outcomes of such patients as a whole have not been investigated. We reviewed a database of 1787 consecutive Ph-neg MPN patients seen at our institution and determined that 2% of Ph-neg MPN patients harbored an alteration involving Chr12 by cytogenetic evaluation. Retrospective chart review revealed that patients with Chr12 abnormalities had a higher likelihood of having myelofibrosis (MF) compared to patients without a Chr12 abnormality, and were more likely to have post-polycythemia vera MF. The most common alterations in Chr12 in MF patients involved 12q13, 12q15, 12q24, and trisomy 12, and >40% of Chr12 Ph-neg MPN patients had cytogenetic evolution. Chr12 abnormalities did not significantly correlate with *JAK2* status, progression to acute myeloid leukemia, or survival, however patients with 12q24 abnormalities trended toward poorer outcomes.

1. Introduction

Myeloproliferative neoplasms (MPNs) result from the clonal proliferation of one or more hematopoietic cell lineages and are characterized by bone marrow fibrosis and extramedullary hematopoeisis. Philadelphia chromosome-negative (Ph-neg) MPN is a subset of MPN patients who do not have a translocation (9;22) and do not have chronic myeloid leukemia. Ph-neg MPN includes polycythemia vera (PV), essential thrombocytosis (ET), myelofibrosis (MF), mastocytosis (MST), and hypereosinophilic syndrome (HES) among others [1]. Approximately 3 per 100,000 people are diagnosed with some form of Ph-neg MPN annually [2]. Frequently Ph-neg MPN is a progressive illness, and some patients will transform into acute leukemia [1]. Chromosome 12 (Chr12) abnormalities have been previously reported in cases of Ph-neg MPN [3–7]. Specific structural abnormalities at 12q15 [6] and 12q24 [8] have been reported for individual patients with primary MF. Disruptions that affect the genes *HMGA2*, an architectural transcription factor, and *SH2B3* (*LNK*), a multifunctional adapter protein, located at the 12q15 and 12q24 loci respectively, have been identified in a handful of cases of Ph-negative MPN [3,4,9,10]. How structural abnormalities of Chr12 contribute to MPN and other cancers is not entirely understood [11–14]. The scope and effects of cytogenetic Chr12 abnormalities in Ph-neg MPN has not been fully characterized. We sought to identify such patients and test whether they had common clinical characteristics, higher rates of transformation to acute myeloid leukemia (AML), and differences in prognosis compared to other Ph-neg MPN patients without chromosome 12 abnormalities (Non-Chr12).

2. Methods

We retrospectively identified all Ph-neg MPN patients (confirmed by bone marrow histology that included karyotype) seen at MD Anderson Cancer Center between 1985 and 2012. Patients were classified and subclassified according to the World Health Organization classification of hematologic malignancies [15]. For karyotypic analysis, unstimulated marrow cells were cultured for 24–72 h, followed by G-banding procedure according to standard techniques in the MD Anderson clinical cytogenetics laboratory. Read out of cytogenetic data was performed by a cytogeneticist, and where possible at least 20 metaphases were examined for each patient. Abnormal clones were defined using current and previous era International System for Human Cytogenetic Nomenclature [16]. We identified patients with aberrations involving Chr12 at the time of presentation to our institution. Abnormalities included translocation breakpoint or disruption, partial or whole deletion, or

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hyperploidy. We further reviewed available medical records, clinical features, and patient outcomes. When available, mutational analysis for JAK2 V617F was carried out by extracting genomic DNA from bone marrow samples, and testing according to institutional standards and as previously described [17]. For all patients in the Ph-neg MPN database, we examined type of MPN, JAK2 status, progression to AML, and overall survival (OS), which was defined as time from diagnosis to death or last follow-up. For each patient with a Chr12 abnormality, we identified demographic data, specific Chr12 abnormality, therapies, and whether they had karyotypic evolution while at our institution, defined as two successive bone marrow biopsies with differing cytogenetic abnormalities. A comparison of binomial proportions was used to detect differences in characteristics between groups. Survival estimates for Chr12 and Non-Chr12 MF patients were generated using Kaplan–Meier curves, and differences assessed using a logrank test. For all analyses, p-value < 0.05 was considered to be statistically significant.

3. Results

The Ph-neg MPN patient database included 1787 patients. A total of 36 patients (2%, 21 male and 15 female) had at least one cytogenetic abnormality in Chr12 (Fig. 1A). Among all Non-Chr12 patients (n = 1751), 945 (54%) were diagnosed with MF, 295 (17%) with ET, 229 (13%) with PV, 126 (7%) with MST, 81 (5%) with HES, and 75 (4%) with unspecified MPN. By comparison, in the Chr12 group (n = 36), 31 (86%) were diagnosed with MF, 1 (3%) with PV, 3 (8%) with HES, and 1 (3%) with unspecified MPN (Fig. 1A). Median age was 61 years (range, 36–83 years) for the Chr12 patients versus 59 years (range, 14–89 years) for the Non-Chr12 patients. A complete list of all Chr12 Ph-neg MPN patients, their clinical characteristics, and the locations of their Chr12 abnormalities is provided in Table 1.

Because a large number of Chr12 patients had MF, we focused on the MF group in greater detail. Of all MF patients in the Ph-neg MPN database (n = 976), 31 (3%) had an abnormality of Chr12 (Fig. 1B). Cytogenetic Chr12 abnormalities occurred at 12q13 (most frequently), 12q15, and 12q24 among others. Six patients had trisomy 12, and 3 patients had a structural abnormality at 12q13 in addition to another Chr12 abnormality (Fig. 1B). Other Chr12 aberrations (some occurring in the same patient) included monosomy 12 (n = 2), and structural breakpoints at 12p13 (n = 1), 12q10 (n = 2), 12q12 (n = 1), 12q21 (n = 1), and 12q23 (n = 1).

We investigated whether the existence of a Chr12 abnormality correlated with a diagnosis of MF, and found that a significantly higher proportion of Chr12 Ph-neg MPN patients were diagnosed with MF compared to Non-Chr12 patients (Fig. 1C, Table 2, p-value < 0.001). In addition, a significantly higher proportion of patients with Chr12 abnormality also had post-PV MF (PPMF, Fig. 1C, Table 2, p-value < 0.001). Among Chr12 MF patients, 11/31 (35%) had PPMF, whereas among Non-Chr12 MF patients 137/945 (14%) had PPMF. There was no significant difference in the proportion of patients who had post-ET MF (PTMF), although a higher fraction (16% versus 13%) had PTMF in the Chr12 group (p-value = 0.11, Fig. 1C, Table 2). In contrast, a significantly higher fraction of patients in the Non-Chr12 group had primary MF (PMF, p-value < 0.01, Fig. 1C, Table 2). Interestingly, 5/12 (42%) patients who had an abnormality at 12q13 had PPMF, which was a significantly higher fraction than in the Non-Chr12 group (p-value = 0.01).

Age, JAK2 status and incidence of leukemic transformation from MF were not significantly different between Chr12 and Non-Chr12 groups (Table 2). The two groups had 80% and 75% of patients

Table 1
Ph-neg MPN patients with Chr12 abnormalities.

Patient N	Age	Sex	Diagnosis	PV/ET	Chr12 loci involved	JAK2	No. prior txs	CG evolution
1	58	M	MF	None	12q24, 12q15	Unk	5	Y
2	83	M	MF	PV	12q24	+	1	N
3	66	M	MPN-U	None	12q24	+	4	N
4	49	F	MF	None	12p13, 12q10	Unk	2	N
5	75	M	MF	None	12q13	Unk	3	Y
6	52	F	MF	None	12q24	Unk	3	N
7	70	F	MF	None	12q24	Unk	2	Y
8	58	M	PV	PV	12q21	+	3	N
9	62	M	HES	None	12q21	Unk	2	Y
10	54	F	MF	None	12q15	Neg	4	Y
11	66	M	HES	None	12q10	Unk	5	N
12	53	F	MF	None	12q13	Unk	0	N
13	71	M	MF	PV	12q13, 12q15	Unk	4	N
14	57	F	MF	ET	12q13, −12, 12p12, 12q21, 12q23	+	6	Y
15	59	M	MF	None	12q13	+	1	Y
16	76	M	MF	PV	−12	+	1	N
17	61	F	MF	PV	12q15	+	4	Y
18	21	M	MF	PV	12q13	+	2	Y
19	57	M	MF	PV	12q24	+	1	N
20	40	M	HES/CEL	None	12q24	Neg	3	N
21	50	F	MF	None	+12	+	1	Y
22	61	F	MF	PV	12q13	+	3	N
23	61	M	MF	ET	12q15	+	2	N
24	35	F	MF	PV	+12	+	1	N
25	58	F	MF	ET	+12	+	1	N
26	56	F	MF	None	+12	Neg	1	Y
27	52	M	MF	PV	+12	+	4	Y
28	32	M	MF	None	+12	+	2	Y
29	24	M	MF	ET	12q12	Neg	2	Y
30	60	F	MF	None	12q13	+	1	N
31	46	M	MF	PV	12q13, 12q24	+	0	N
32	36	F	MF	None	12q13	Neg	4	N
33	47	F	MF	PV	12q13	+	2	N
34	63	M	MF	None	12q24	Neg	0	N
35	51	M	MF	PV	12q24	+	0	N
36	63	M	MF	ET	12q13	Neg	3	N

Patient N, patient number; PV, polycythemia vera; ET, essential thrombocytosis; No. prior txs, number of prior therapies; CG, cytogenetic; MPN-U, unspecified myeloproliferative neoplasm; HES, hypereosinophilic syndrome; CEL, chronic eosinophilic leukemia.