

Increased risk of lymphoid neoplasm in patients with myeloproliferative neoplasm: a study of 1,915 patients

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ABSTRACT

Within a cohort of 1,915 consecutive patients with myeloproliferative neoplasm followed for a median time of 5.2 years (range 0-33.3), we investigated the occurrence of lymphoid neoplasm with the aim of defining this risk and to investigate the role of genetic predisposing factors. We identified 22 patients with myeloproliferative neoplasm who developed lymphoid neoplasm over their lifetime. We found that the risk of developing lymphoid neoplasm was 2.79-fold higher (95% CI, 1.80-4.33; $P < 0.001$) than that of the general Italian population. A tag SNP surrogate for *JAK2* GGCC haplotype was used to clarify a potential correlation between lymphoid-myeloid neoplasm occurrence and this genetic predisposing factor. As we did not find any difference in GGCC haplotype frequency between patients with both myeloid and lymphoid neoplasm and patients with myeloid neoplasm, *JAK2* GGCC

haplotype should not be considered a genetic predisposing factor. No difference in familial clustering was observed between the two groups.

Key words: polycythemia, thrombocythemia, myelofibrosis, lymphoid, familial.

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Introduction

Myeloproliferative neoplasm (MPN), including polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) are rare disorders with an annual incidence rate of 2.1 per 100,000 person-years.¹ The course of myeloproliferative neoplasm is complicated mainly by vascular events and transformation to myelofibrosis or leukemia; secondary malignancies may occur with a low incidence.² A previous study demonstrated that patients with myeloproliferative neoplasm have a 3.44-fold higher risk of developing lymphoid neoplasm (LPN) than the general population.³ On this basis, a common genetic susceptibility may be taken into account. In a familial-MPN setting, first-degree relatives of patients with myeloproliferative neoplasm have a 5- to 7-fold higher risk of developing these diseases,⁴ and an increased risk of secondary malignancies.⁵ Likewise, first-degree relatives of patients with chronic lymphocytic leukemia or lymphoplasmacytic lymphoma are at increased risk for lymphoid neoplasm.^{6,7}

Inherited genetic factors with a role in the development of sporadic myeloproliferative neoplasm have been recently defined.⁸⁻¹⁰ More than 80% of *JAK2* (V617F) mutations are

acquired on a particular *JAK2* gene haplotype, the GGCC or 46/1 haplotype. This sequence variant of the *JAK2* gene confers susceptibility to *JAK2*-mutated myeloproliferative neoplasm⁸⁻¹⁰ and to *JAK2*-wild type myeloproliferative neoplasm.¹¹

To define the association of myeloproliferative neoplasm and lymphoid neoplasm, we explored our myeloproliferative neoplasm database to identify those patients with a well defined diagnosis of lymphoid neoplasm. In addition, we investigated whether GGCC *JAK2* haplotype and familial clustering are overrepresented in LPN-MPN patients.

Design and Methods

Study population

This study includes 1,915 consecutive patients with polycythemia vera, essential thrombocythemia and primary myelofibrosis, post-essential thrombocythemia and post-polycythemia vera myeloid fibrosis recorded in our myeloproliferative neoplasm database. Patients with diagnosis of myeloproliferative neoplasm not otherwise specified were excluded from the study. All patients were followed at the Division of Hematology, Fondazione I.R.C.C.S. Policlinico San Matteo, University of Pavia, Italy from 1970 to 2009. Diagnosis of myeloproliferative neoplasm was made according to criteria in use at

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the time of first observation.¹²⁻¹⁷ The International Working Group on MPNs Research and Treatment (IWG-MRT) criteria were used to define post-essential thrombocythemia and post-polycythemia vera myeloid fibrosis.¹⁸ Clinical charts of patients recorded to have lymphoid neoplasm were reviewed to obtain a final diagnosis in agreement with the WHO criteria. Among 1,915 myeloproliferative neoplasm cases, information on familial history of myeloproliferative neoplasm was obtained in 1,050 (54.8%) patients available for the interview. The study was approved by the Institute Review Board of the Fondazione I.R.C.C.S. Policlinico San Matteo and the procedures followed were in accordance with the 1975 Declaration of Helsinki, as revised in 2000. Samples for molecular analysis were obtained following patients' informed written consent.

JAK2 (V617F) analysis and SNP genotyping

The *JAK2* (V617F) mutational status was assessed on peripheral blood granulocytes using a quantitative real-time polymerase chain reaction-based allelic discrimination assay.¹⁹ A tag SNP (rs10974944) surrogate for the GGCC haplotype (GG or GC = GGCC haplotype; CC=not GGCC haplotype) was genotyped on T-lymphocyte DNA.²⁰ The commercially available C_31941696 Taqman assay (Applied Biosystems) was used on the Rotor-Gene™ 6000 real-time PCR instrument in a final volume of 10 µL according to the manufacturer's procedure. We genotyped 694 (36%)

patients and 203 controls: 43 healthy subjects, 126 with *JAK2* (V617F)-negative secondary erythrocytosis and 34 with *JAK2* (V617F)-negative secondary leukocytosis.

Analysis of VH gene usage and mutations

The analysis of immunoglobulin heavy chain gene variable, diversity and joining (IGHV-D-J) genes was performed on mononuclear cells obtained from peripheral blood or bone marrow samples after isolation on a Ficoll gradient, as previously described.²¹ We studied 8 of 10 patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and chronic B lineage lymphoproliferative disorder (B-LPL) for whom DNA was available in order to evaluate whether CLL/SLL/B-LPL associated to myeloproliferative neoplasms display a particular repertoire of IGHV genes.

Statistical analysis

For the aims of this study, only lymphoid neoplasms occurring after the diagnosis of myeloproliferative neoplasm were considered. The period at risk was defined for each patient from the date at diagnosis of myeloproliferative neoplasm to the date of occurrence of lymphoid neoplasm, date of death, or date of the last follow up, whichever came first. The relative risk of lymphoid neoplasms was expressed as a standardized incidence ratio (SIR), defined as the ratio between observed and expected cases. The

Table 1. Clinical characteristics of the 22 patients with myeloid and lymphoid neoplasm (LPN-MPN).

Patient code	Gender (M/F)	MPN	Age at MPN (years)	LPN	Age at LPN (years)	JAK2 (V617F)	JAK2 haplotype	VH gene usage and mutational status	Familial history of MPN
S70A97SM	M	ET	68	SLL	77	30	GC	NA	No
S12A2SM	M	ET	44	SLL	55	0	CC	IGHV3-48 Mutated	No
S167A6SM	M	ET	34	CLL	50	0	GC	IGHV1-69 Unmutated	Yes
S41A85SM	M	ET	44	T-LBL	57	NA	NA	--	No
S82A7SM	M	ET	39	Chronic B-LPL	53	0	CC	IGHV3-49 Mutated	No
S23A78SM	F	ET	44	DLBCL	58	NA	NA	--	No
S2A8SM	F	ET	63	Chronic B-LPL	64	2.2	GG	IGHV3-48 Unmutated	Yes
S66A99SM	M	ET	31	CLL	41	8.7	CC	IGHV1-46 Mutated	No
S24A6LNH	M	ET	45	DLBCL	58	0	GC	--	No
S90A4SM	F	ET	71	DLBCL	83	22.4	CC	--	No
S69A8SM	M	ET	70	DLBCL	72	15.2	GC	--	No
S29A97SM	F	ET	56	Chronic B-LPL	69	0	CC	NA	No
S15A93V	M	PV	65	DLBCL	75	NA	NA	--	No
S57A89SM	F	PV	36	MM	60	70.7	GC	--	No
S8A93V	F	PV	66	MM	74	NA	NA	--	No
S7A96V	M	PV	69	CLL	75	NA	NA	Unmutated IGHV1-8	No
S5A82V	M	PV	41	DLBCL	64	NA	NA	--	No
S2A0V	M	PV	70	DLBCL	79	35	GC	--	No
S131A4SM	M	PMF	59	SLL	66	15.4	CC	Mutated IGHV4-34	No
S55A51*	F	PMF	66	Chronic B-LPL	66	13.8	CC	Mutated IGHV2-5	Yes
S2000A9V [§]	M	PV	90	FL	64	21.6	GC	--	No
S1A75HCL [§]	M	PV	81	HCL	50	46.8	GG	--	No

M: male; F: female; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; SLL: small lymphocytic lymphoma; CLL: chronic lymphocytic leukemia; TLBL: T lymphoblastic lymphoma; Chronic B-LPL, B chronic lymphoproliferative disorder; DLBCL: diffuse large B-cell lymphoma; MM: multiple myeloma; FL: follicular lymphoma; HCL: hairy cell leukemia; NA: not available; VH: variable heavy chain. *In this case diagnosis of MPN and LPN were concomitant. [§]In these 2 cases the diagnosis of LPN preceded the onset of MPN.

Table 2. Genotyping results for the *JAK2* GGCC tag SNP rs10974944.

Case population	Control population	Frequency of GGCC alleles (case population)	Frequency of GGCC alleles (control population)	Odds ratio (95% CI)	P value
LPN-MPN (n=16)	MPN (n=678)	0.344	0.400	0.78 (0.34-1.72)	0.59
LPN-MPN V617F+ (n=11)	MPN V617F+ (n=442)	0.409	0.438	0.89 (0.33-2.28)	0.83
LPN-MPN (n=16)	Control group (n=203)	0.344	0.268	1.43 (0.60-3.22)	0.41
MPN (n=678)	Control group (n=203)	0.400	0.268	1.82 (1.42-2.35)	<0.001

MPN: myeloproliferative neoplasm; LPN: lymphoid neoplasm; V617F+, *JAK2* (V617F) positive MPN; CI: confidence interval.

expected number of lymphoid neoplasm cases was estimated using sex and age incidence rates reported by AIRTUM (Associazione Italiana Registri Tumori) for Northern Italy in the period 2000-2003, applied to the corresponding person-years at risk. When investigating the effect of familial predisposition and GGCC *JAK2* haplotype, all lymphoid neoplasm cases, i.e. occurring either before or after myeloproliferative neoplasm, were taken into account.

Results and Discussion

The myeloproliferative neoplasm database included 1,915 patients with myeloproliferative neoplasm: 651 (34%) polycythemia vera, 848 (44%) essential thrombocythemia, 334 (18%) primary myelofibrosis and 82 (4%) secondary myelofibrosis. Among these, 22 (1.1%) patients developed lymphoid neoplasm over their lifetime: 20 had lymphoid neoplasia after myeloproliferative neoplasm and 2 before. Clinical characteristics of patients with LPN-MPN are reported in Table 1. All but 3 patients received cytoreductive therapy: hydroxyurea alone (n=8), pipobroman alone (n=6), or more than one cytoreductive treatment (n=5). After a median follow up of 10.2 years (range 0.1-23.5 years), 8 patients died because of progressive lymphoid neoplasm (n=4), blastic phase of myeloproliferative neoplasm (n=1) or unknown causes (n=3). In lymphoid neoplasm studies, variable region genes were mutated in 5 of 8 cases. Although no biased IGVH gene usage was observed, 2 patients carried IGHV1-69 and IGHV4-34, belonging to the immunoglobulin repertoire overrepresented in chronic lymphocytic leukemia.²²

The median follow up of 1,915 patients was 5.2 years (range 0-33.3 years). Overall, the risk of myeloproliferative neoplasm patients developing lymphoid neoplasm was 2.79-fold higher (95% CI: 1.80-4.33; $P<0.001$) than in the general population. This risk was higher than expected both in males (SIR 3.23, 95% CI: 1.88-5.57; $P<0.001$) and in females (SIR 2.23, 95% CI: 1.06-4.68; $P=0.029$).

Considering the effect of age on SIR, we found that the SIR was 6.16 (95% CI: 3.2-11.84; $P<0.001$) in patients aged under 50 and 1.93 (95% CI: 1.07-3.49; $P=0.026$) in patients aged over 50. The median time from myeloproliferative neoplasm diagnosis to lymphoid neoplasm occurrence was 10.5 years (range 0-23.4 years). Cumulative incidence of lymphoid neoplasm was calculated considering death for other causes as a competing risk (Figure 1). Considering data available in the literature, we may state that, at least in

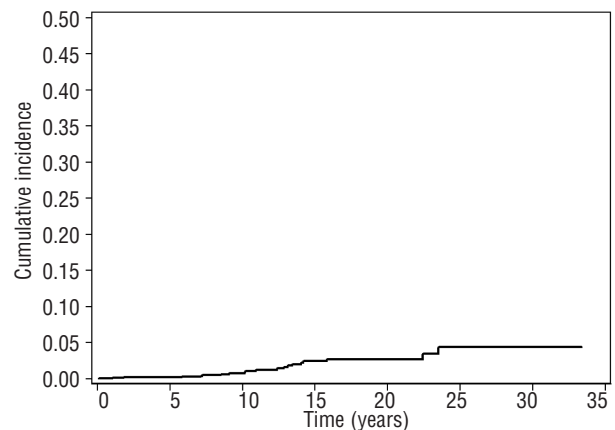


Figure 1. Cumulative incidence of LPN. The figure shows the cumulative incidence of LPN considering the death for other causes as a competing risk.

Italy, the 10-year risk of lymphoid neoplasm in myeloproliferative neoplasm patients ranges from 0.7% (this study) to 2.96%.³ Heterogeneity of the two Italian cohorts including age (55.6 years in this study and 59 years in the Vannucchi study)³ may explain this discrepancy.

The *JAK2* (V617F) mutational status was available in 16 (73%) of 22 patients with LPN-MPN: 11 (69%) carried the mutation and 5 (31%) were wild type. There was no significant difference in occurrence of lymphoid neoplasm between *JAK2* (V617F)-positive and *JAK2* (V617F)-negative patients, even after stratification for diagnosis. This is in contrast with a prior study³ that did not report lymphoid neoplasms among patients with *JAK2* wild-type myeloproliferative neoplasm. Our finding on a large cohort implies that susceptibility genes other than *JAK2* (V617F) might favor the genetic instability predisposing to both lymphoid neoplasm and myeloproliferative neoplasm.

Recently, a specific constitutional *JAK2* haplotype, the GGCC or 46/1 haplotype, has been demonstrated to confer susceptibility to *JAK2* (V617F)-positive myeloproliferative neoplasm⁸⁻¹⁰ and *JAK2*-wild type myeloproliferative neoplasm.¹¹ To evaluate whether the *JAK2* GGCC haplotype might represent the genetic predisposition to develop both myeloproliferative neoplasm and lymphoid neoplasm, we compared the frequency of the high-risk G allele among 16

LPN-MPN patients for whom DNA was available: 678 myeloproliferative neoplasm patients and 203 control subjects (Table 2). No difference was observed between patients with LPN-MPN and patients with myeloproliferative neoplasm (OR 0.78; 95% CI: 0.34-1.72; $P=0.59$), even when considering only the *JAK2*-mutated patients (OR 0.89; 95% CI: 0.33-2.28; $P=0.83$). Thus, the risk of developing lymphoid neoplasm is not associated with the *JAK2* GGCC haplotype.

The GGCC haplotype was more frequent in myeloproliferative neoplasm patients than in the control population (OR 1.82; 95% CI: 1.42-2.35; $P<0.001$), confirming that the *JAK2* GGCC haplotype is overrepresented in myeloproliferative neoplasm patients in agreement with recent literature.⁸⁻¹¹

To look for clinical arguments in favor of an inherited susceptibility to hematologic neoplasia we focused on the 1,050 myeloproliferative neoplasm patients interviewed about familial history.

We compared the prevalence of familial cases reported in the 22 patients with LPN-MPN and that observed in the remaining 1,028 patients without lymphoid neoplasm. The presence of another relative affected with myeloproliferative neoplasm within the same pedigree was referred in 3 out of the 22 (13.6%) patients with LPN-MPN and in 65 out of 1,028 (6.3%) patients with myeloproliferative neoplasm. No difference in terms of familial clustering was observed between LPN-MPN and myeloproliferative neoplasm (OR 2.33; 95% CI: 0.43-8.25; $P=0.16$). Further studies comparing the total occurrence of secondary malignancies between familial and sporadic myeloproliferative neoplasm might clarify whether this 2.33-fold higher Odds Ratio reaches a statistical significance and whether it's reasonable to suppose a genetic predisposition to somatic mutagenesis. The prevalence of familial cases among myeloproliferative neoplasm patients without occurrence of lymphoid neoplasm is consistent with the 7.6% previously published.²³

In 2 patients the diagnosis of lymphoid neoplasm preceded the onset of myeloproliferative neoplasm. They developed *JAK2* (V617F)-positive polycythemia vera three decades after the initial diagnosis of hairy cell leukemia and of follicular non-Hodgkin's lymphoma, respectively. If a

genetic susceptibility exists, one should hypothesize a random order of onset of the myeloid or of the lymphoid neoplasm and then should expect an equal frequency of patients with myeloproliferative neoplasm who develop lymphoid neoplasm or *vice versa*. The low number of myeloproliferative neoplasm patients with a previous lymphoid neoplasm reported in our study may be due to a more aggressive behavior of lymphoid neoplasms, so that patients die before myeloproliferative neoplasm develops. The distribution of myeloproliferative neoplasm types among patients with LPN-MPN supports this hypothesis. The highest number of lymphoid neoplasm was observed among patients with essential thrombocythemia ($n=12$), whose survival is generally longer due to the good prognosis of this disease.² Conversely, the lowest number of lymphoid neoplasm was observed in patients with primary myelofibrosis ($n=2$), whose life expectancy is not long enough to develop secondary lymphoid neoplasms.²⁴

In conclusion, patients with myeloproliferative neoplasm have a higher risk of developing lymphoid neoplasm than the general population. No difference in terms of familial clustering was observed between LPN-MPN and myeloproliferative neoplasm. We did not find a statistical association between the *JAK2* GGCC haplotype and LPN-MPN. These results are based on a low number of patients with both myeloproliferative neoplasm and lymphoid neoplasm, due to the rare occurrence of both disorders. Moreover familial history and *JAK2* haplotype were available only in a subgroup of patients. Further studies of larger patient cohorts, including thorough investigation into possible familial history and genotyping for *JAK2* haplotype, are needed to definitively rule out an association.

Authorship and Disclosures

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