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TO THE EDITOR:

Characteristics of patients with myeloproliferative neoplasms with lymphoma, with or without JAK inhibitor therapy

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It is well known that patients with cancer may subsequently develop secondary/therapy-related neoplasms, generally exhibiting poorer prognosis than their de novo counterparts.[1] Among patients with myeloproliferative neoplasms (MPN), there may be a higher rate of second malignancies before, concomitant with, or after their MPN diagnosis as compared with the general population[2-9] (Table 1). We recently reported (and others confirmed) the association of lymphoid malignancies coexistent with an MPN diagnosis and found this to be an overall rare phenomenon that did not predict for worse clinical outcomes among MPN patients.[10] The incidence and relative risk of post-MPN lymphoid neoplasms has been evaluated, and a 1.4- to 5-fold higher risk in this population has been identified, regardless of therapy received (Table 1). A recent important report in this area raises the possibility that those patients with MPN treated with a Janus kinase (JAK) inhibitor class of therapies may have a markedly higher rate of development of a subsequent lymphoma than patients who did not receive these therapies.[11] Given the paucity of data sets that specifically focus on those patients with MPN treated with a JAK inhibitor subsequently diagnosed with a lymphoma, we sought to determine the characteristics and outcomes of this particular subset of patients in our large patient database.

We performed a comprehensive, multidisciplinary, retrospective chart review of all patients with diagnosis of MPN or lymphoma treated at our institution from May 1965 to November 2018. In order to ensure that all possible patients were captured for

Table 1. Major studies of lymphoproliferative neoplasms in patients with MPN

Study	Study type	LPN before, concurrent, or after MPN	RR or SIR/SPR for secondary malignancy	Patients with MPN	No. of LPNs detected	No. with MPN first	No. with LPN first	No. with concurrent disease
Vannucchi et al[18]	Retrospective	After	3.44	820	11	N/A	N/A	N/A
Masarova et al[10]	Retrospective	Before, concurrent, and after	N/A	9866	15	15	16	2
Masarova et al[4]	Retrospective	After	N/A	417	8	N/A	N/A	N/A
Frederiksen et al[3]	Retrospective	After	5	6203	152*	N/A	N/A	N/A
Palandri et al[5]	Retrospective	Concurrent and after	N/A	499	8	2	N/A	6
Rumi et al[6]	Retrospective	After	2.79	1915	22	N/A	N/A	N/A
Pettersson et al[19]	Retrospective	Before	1.49	2213	N/A	N/A	30*	N/A
Brunner et al[9]	Retrospective	After	2.27-3.14	20 250	124	N/A	N/A	N/A
Landtblom et al[7]	Retrospective	After	2.6	9379	90	N/A	N/A	N/A
Marchetti et al[8]	Review	Before, concurrent, and after	N/A	214	214	105	43	65

LPN, lymphoproliferative neoplasms; N/A, not applicable; RR, relative risk; SIR/SPR, standard incidence ratio/standard prevalence ratio.
*Lymphoid and myeloid malignancies were not separated.

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Table 2. Characteristics of patients, MPN, and subsequent lymphoma

Patient no.	Sex	MF Dx date	Prior MPN	Molecular (allele %)	LDH at MF Dx	Marrow fibrosis grade	Cytogenetics at time of MF Dx	Prior MPN therapies before JAK inhibitor	JAK inhibitor received	JAK inhibitor prior to lymphoma?	Lymphoma Dx date	Age at lymphoma Dx	Lymphoma stage	Lymphoma subtype	Lymphoma treatment	OS from lymphoma Dx
1	M	8/14/2000	No	Not done	569	MF-2	Diploid	HU	N/A	N	3/22/2010	62	I	Follicular lymphoma, grade 3A	Observation	11 mo
2	M	3/26/2012	No	JAK2 (46.4%)	1107	MF-2	Diploid	None	N/A	N	4/12/2012	62	IV	Enteropathy associated TCL	Observation	NR
3	F	7/23/2013	PV	JAK2 (42.1%)	949	MF-2	46,XX,t(9;15) (p24;q15)	HU+ phlebotomy	N/A	N	9/3/2013	63	IV	TCL, anaplastic, ALK$^-$	CHOP	1.6 mo
4	M	3/9/2010	PV	JAK2 (86%)	916	MF-2	46,XY,del(20) (q11.2q13.3)	None	Len + Rux	Y	7/13/2015	54	IV	DLBCL	R-EPOCH	Lost to follow-up
5	F	11/30/2010	No	Triple-negative MF	763	MF-2	Diploid	None	Rux	Y	1/15/2017	69	Unknown	NHL (scalp)	Lost to follow-up	Lost to follow-up
6	M	2/21/2006	No	Not done	1635	MF-2	Diploid	None	CEP-701	Y	8/7/2014	49	IV	DLBCL	R-CHOP/HD MTX	5.5 mo
7	M	6/27/2008	PV	JAK2 (82%)	1134	MF-3	46,XY,del(13) (q12q14)	HU	Rux	Y	2/2/2010	66	IV	MCL	R-hyper-CVAD/ R-MTX/Ara-C	67 mo
8	M	11/20/2009	No	JAK2 (87.1%)	2463	MF-3	46,XY,del(20) (q11.2q13.3)	HU	CYT387	Y	5/2/2017	77	IV	MCL	R	5.7 mo
9	M	12/23/2010	PV	JAK2 (87.85%)	1451	Not done	Diploid	Phlebotomy	AZD1480	Y	8/10/2018	72	II	DLBCL	R-CHOP	NR

CHOP, cyclophosphamide, hydroxydaunorubicin (doxorubicin or adriamycin), oncovin (vincristine), prednisone; DLBCL, diffuse large B-cell lymphoma; Dx, diagnosis; F, female; HU, hydroxyurea; Len, lenalidomide; M, male; MCL, mantle cell lymphoma; MTX, methotrexate; NHL, non-Hodgkin lymphoma; NR, not reached; R-EPOCH, rituximab, etoposide phosphate, prednisone, vincristine sulfate (oncovin), cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin); R-hyper-CVAD, rituximab plus hyper-fractionated cyclophosphamide, vincristine sulfate, doxorubicin hydrochloride, and dexamethasone; Rux, ruxolitinib; TCL, T-cell lymphoma.

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retrospective analysis, we queried 4 separate institutional patient data sets (cross-checked, with rigorous, continuous updated follow-up/outcomes) in the Departments of Leukemia, Pharmacy, Lymphoma, and Pathology. Overall, we identified 17 570 patients with lymphoma and 2583 patients with a diagnosis of MPN (including essential thrombocythemia [ET], polycythemia vera [PV], and myelofibrosis (MF; either primary or secondary to ET/PV). We then identified patients with *both* a confirmed diagnosis of MPN (ET, PV or MF) and lymphoma by World Health Organization criteria[12,13] and age ≥18 years for a total of 21 patients (n = 13 lymphoma diagnosis prior to MPN, n = 9 lymphoma diagnosis after MPN). The focus of this analysis is the 9 patients with lymphoma diagnosed after the MPN diagnosis.

In total, we identified 2583 patients with MPN, including 1617 patients with MF (median follow-up time, 26 months; range, 0-348 months) and 966 patients with ET or PV (median follow-up time, 24 months; range, 0-345 months). Among the patients with MF, only 9 out of 1617 (0.56%) developed a subsequent lymphoma after the MF diagnosis. In the MF cohort (n = 1617), 623 patients had exposure to a JAK inhibitor and 994 did not. Among the 9 patients who went on to develop lymphoma, 6 had previous exposure to a JAK inhibitor and 3 did not, with a *P* value between the 2 groups that was not statistically significant (.082). In contrast, we found a slightly higher number of patients (n = 13) with a lymphoma diagnosis *before* the MF diagnosis.

The median age at the time of MF diagnosis among the 9 total patients was 63 years (range, 41-70 years); the median age of the 6 patients who had previous exposure to a JAK inhibitor was 64 years (range, 41-70) (*P* = .395, with no difference between the 2 groups). The median time from first exposure of a JAK inhibitor to the development of lymphoma was 3.5 years (range, 1.7-7.3 years). Three of the 6 patients who received JAK inhibitors were treated with ruxolitinib, and the remaining 3 patients were treated with other JAK inhibitors (Table 2) (CEP-701, n = 1; CYT387 [momelotinib], n = 1; and AZD1480, n = 1).

We next examined our ET and PV cohorts, given that JAK inhibitors have also been investigated in clinical trials in ET[14,15] and ruxolitinib is now approved in the advanced PV setting posthydroxyurea.[16] A total of 966 patients comprised the overall ET/PV cohort, with a median follow-up time of 24 months (range, 0-345 months) and a median age of 52 years (range, 14-89 years) at diagnosis. Sixty patients had prior JAK inhibitor therapy; none of these 60 patients developed lymphoma after a median follow-up time of 51 months (range, 0-263 months). We did note, however, that 5 out of 906 patients who did not receive a JAK inhibitor developed lymphoma (0.55%); the *P* value not significant between these 2 groups.

Among the 6 patients with MF who were treated with a JAK inhibitor, we observed DLBCL (n = 3), MCL (n = 2), and other NHL (scalp) (n = 1). Among the 3 patients without prior JAK inhibitor therapy, we observed T-cell lymphoma (n = 2) and follicular lymphoma grade 3A (n = 1). The median age was 63 years (range, 41-70 years) at MF diagnosis and 68 years (range, 50-78 years) at lymphoma diagnosis. The majority of the patients diagnosed with lymphoma were male (Table 2). Though limited by a small sample size, the survival was relatively short following the lymphoma diagnosis for the majority of patients. The overall small numbers of patients and heterogeneity in lymphoma subtypes (including both B- and T-cell lymphomas) impairs our ability to draw any conclusions regarding the potential impact of JAK inhibitors on lymphomagenesis and outcomes.

In this large database review, we found no statistically significant difference in the incidence of a subsequent lymphoma diagnosis in patients with MPNs when comparing those who received prior JAK inhibitor therapy and those who did not. It is important to investigate this further, as we demonstrate different findings than Porpaczy et al.[11] In the MPN literature, it is well known that there is a coincidence of other malignancies, including both solid tumors and lymphoid malignancies (Table 1). These reports did not have specific focus on JAK inhibitor therapy, however. In our analysis, importantly, we focused on this particular question, in a database consisting of 2583 patients with MPN (PV, ET, and MF), which represents approximately twofold more patients than in the Porpaczy et al study.[11] Similar to that report, we also demonstrate a relatively short onset time to lymphoma development while on JAK inhibitor therapy of median 3.5 years; we also demonstrate a standard median age at the diagnosis of MF (63 years), and most of the patients identified with lymphoma to be *JAK2* V167F mutated (6/9 [67%]). In contrast with the Porpaczy et al study, we demonstrated no significant increase in lymphoma rates in the JAK-inhibitor–treated population as compared with the non-JAK-inhibitor–treated group. Additionally, the rate of lymphoma after MPN diagnosis in our series is much lower (9/1617 [0.56%]) than that reported by Porpaczy et al (5.8% to 9.7%). There are several possible reasons for these 2 discrepant series. One, we have assembled a much larger data set, and larger numbers may diminish the relative effect of individual case observations. Second, the median follow-up time is critical to note, as in the present study, it is 26 months (0-348 months) in the MF cohort, and thus longer follow-up over time will be warranted. Additionally, in the Porpaczy et al study, it is notable that 2 out of 6 lymphoma cases (33%) received pipobroman as MF therapy prior to the lymphoma diagnosis, whereas none of our patients received prior pipobroman in the current study. (In a long-term follow-up study of MPN patients treated with pipobroman, the 10-year risk of second cancers was 4% to 8% with pipobroman.[17]) Finally, there may be important environmental, geographic, or other hitherto undetermined demographic factors that could be different in American vs European cohorts worthy of further analysis.

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Authorship

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Footnote

There is a *Blood* Commentary on this article in this issue.

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