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Association of lymphoid malignancies and Philadelphia-chromosome negative myeloproliferative neoplasms: Clinical characteristics, therapy and outcome

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ABSTRACT

The co-occurrence of myeloproliferative and lymphoproliferative neoplasms (MPN/LPN) has been reported, mostly in case reports. The aim of this study was to assess the characteristics and clinical course of the coexistent diseases. Among 9866 patients who presented to our institution from 1960 to 2014, 34 (0.3%) were diagnosed with MPN/LPN. LPN was diagnosed first in 16 patients, second in 15, and at the same time in 3. The time to secondary malignancy was longer when LPN was diagnosed first (119 vs 98 months). Myelofibrosis (41%), polycythemia vera (24%), and essential thrombocythemia (18%) were the most common MPNs, and non-Hodgkin lymphoma (50%) and chronic lymphocytic leukemia (32%) were the most common LPNs. Seventy-three percent of patients treated for MPN and 72% of those treated for LPN achieved a complete response. After a median follow-up from MPN diagnosis of 84 months, 16 patients are alive and 18 died (4 related to MPN and 2 LPN). Coexistent MPN/LPN is a rare event that does not appear to predict worse outcomes. Treatment choice is generally oriented towards controlling the prevalent disease; the other malignancy may influence treatment strategies in selected cases.

1. Introduction

Myeloproliferative neoplasms (MPN) are a group of heterogeneous, relatively indolent neoplastic disorders, encompassing essential thrombocythemia (ET), polycythemia vera (PV), and myelofibrosis (MF). Patients with ET and PV have life expectancies that are comparable with that of age-matched healthy individuals. The clinical course of MF is more aggressive, with a median survival of 5–7 years [1]. Patients with ET and PV have an increased risk of vascular events, as well as increased risk of transformation into myelodysplastic syndrome or MF. All 3 MPNs (ET, PV, MF) may develop into acute leukemia [2] or more rarely the patients may develop a second solid or hematologic malignancy. Studies suggest that the incidence of second tumor of the hematopoietic system is higher in patients with MPN [3,4] however, the coexistence of an MPN and a lymphoproliferative neoplasm (LPN) is still believed to be a rare finding, reported sporadically in the literature. Moreover, very few retrospective studies of the clinical behavior of these coexistent disorders have been published. A report by Palandri et al. described only non-Hodgkin lymphoma (NHL) in the context of MPN [5], and Laurenti et al. described the coexistence of CLL and an MPN [6]. Both authors concluded that the coexistence of an LPN and an MPN is an uncommon, occasional event and in most cases, the coexistent diseases have a fairly indolent clinical behavior. In a review of the literature through December 2014, we found over 200 cases describing various subtypes of coexistent LPN and MPN (LPN/MPN), most of which were single case reports.

In this study, we aimed to define the prevalence of MPN/LPN, the clinicobiological characteristics and clinical course of both diseases, as well as the possible influence of treatment on the course of the second disease.

2. Design and methods

We reviewed the entire MPN ($n = 1475$) and CLL ($n = 8391$) databases of patients referred to MD Anderson Cancer Center between 1960 and 2014. We identified 34 patients diagnosed with both MPN and LPN during their lifetime. We retrospectively collected and analyzed all relevant demographic, clinical, and

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Table 1
Clinicobiological characteristics of all patients with MPN/LPN: stratified by MPN subtype (PART I.), and LPN timing (PART II. + III.).

PART I.	Total	ET	PV	MF	MPN-U	HES
MPN and CLL database, *n*	1475 and 8391	265	178	871	72	89
MPN/LPN *n*, (%)	34 (0.3)	6 (1)	8 (3)	14 (2)	4 (6)	2 (2)
LPN type, *n*, (%)						
Non-Hodgkin's lymphoma (NHL)	17 (50)	4 (66)	5 (63)	6 (43)	2 (50)	0
Chronic lymphocytic leukemia (CLL)	11 (33)	2 (33)	2 (25)	5 (36)	1 (25)	1 (50)
Hodgkin's lymphoma (HL)	3 (9)	0	1 (12)	1 (7)	0	1 (50)
Multiple myeloma (MM)	3 (9)	0	0	2 (14)	1 (25)	0
LPN timing, *n* (%)						
First dx	16 (49)	0	2 (25)	9 (64)	3 (75)	2 (100)
Second dx	15 (42)	5 (83)	6 (75)	3 (21)	1 (25)	0
Simultaneous dx	3 (9)	1 (17)	0	2 (14)	0	0
Sex, *n* (%)						
Male	20 (59)	4 (67)	5 (63)	7 (50)	3 (75)	1 (50)
Female	14 (41)	2 (33)	3 (37)	7 (50)	1 (25)	1 (50)
Race, *n* (%)						
Caucasian (Cauc)	31 (91)	6 (100)	7 (88)	12 (86)	4 (100)	2 (100)
Black (Bl)	2 (6)	0	1 (12)	1 (7)	0	0
Hispanic (Hisp)	1 (3)	0	0	1 (7)	0	0
Median age at MPN dx, [range] months	56 [16–79]	46.5 [16–60]	60 [45–71]	62 [34–79]	53 [31–55]	64 [62–66]
PS, *n* (%)						
0–1	32 (94)	6 (100)	8(100)	14 (100)	2 (50)	2 (100)
2	2 (6)	0	0	0	2 (50)	0
Splenomegaly, *n* (%)	13 (33)	2 (33)	3 (38)	8 (57)	2 (50)	1 (50)
JAK2 positive, *n* (%)	14/24 (42)	1/3 (17)	8/8 (100)	3/10 (21)	2/3 (50)	1/1 (100)
Abnormal karyotype, *n* (%)	15 (47)	2 (33)	5 (63)	6 (46)	1 (25)	1 (50)

PART II.	LPN Prior to MPN, *n* = 16 (47%)	LPN After MPN, *n* = 15 (44%)	Simultan. LPN and MPN, *n* = 3 (9%)
LPN type, *n*, (%)	6 NHL, 5 CLL, 3 HL, 2 MM	1 NHL, 4 CLL, 1 MM	1 NHL, 2 CLL
MPN type, *n*, (%)	2 PV, 9 MF, 3 MPN, 2 HES	5 ET, 6 PV, 3 MF, 1 MPN	1 ET, 2 MF
Male/Female Ratio	1.0 (8/8)	2.0 (10/5)	2.0 (2/1)
Race, *n* (%)	15 Cauc, 1 Bl	13 Cauc, 1 Bl, 1 Hisp	3 Cauc
Median age at MPN dx, [range] months	51.5 (34–77)	67 (22–84)	59 (56–72)
Median age at LPN dx, [range] months	51 (8-76)	53 (16–71)	59 (56–72)
PS 2, *n* (%)	0	2 (13)	0
Splenomegaly, *n* (%)	5 (31)	6 (40)	1 (33)
JAK2 positive, *n* (%)	6/10 (60)	8/11 (72)	1/2 (50)
Abnormal karyotype, *n* (%)	6/15 (40)	8/15 (53)	1/3 (33)

PART III.	LPN Prior to MPN, *n* = 16 (47%)	LPN After MPN, *n* = 15 (44%)	Simultan. LPN and MPN, *n* = 3 (9%)
Median time to 2nd DX, months (range)	98 (4.7–439)	119 (1–552)	NA
Median follow up [MPN], months, (range)	34 (0.5–180)	151 (91–585)	87 (6.8–88)
Median follow up [presentation], months (range)	36 (1–204)	44 (2–125)	31.8 (5.8–86)
Median observation time [1st DX], months (range)	150 (12–470)	151 (91–585)	87 (6.8–88)
Median OS [MPN], months (range)	42 (1.7–181)	132 (78–585)	6.8
Median OS [LPN], months (range)	144 (12–422)	26 (9.4–128)	6.8
Overall status—Alive/Death, *n* (%)	8/8 (50/50)	6/9 (40/60)	2/1 (67–33)

therapeutic data by reviewing the patients' medical records, with special attention given to the LPN diagnosis and its timing with respect to the MPN diagnosis. For each patient, the follow-up time was defined as the date of MPN diagnosis to the date of death or last follow-up, whichever came first. The observational time was defined as the date of first diagnosis (MPN or LPN) to the date of death or last follow-up.

3. Results

Between 1960 and 2014, 9866 patients diagnosed with MPN ($n = 1475$) or CLL ($n = 8391$) presented to our institution. MF was the most common diagnosis ($n = 871$), followed by PV ($n = 178$) and ET ($n = 265$). Among these, 34 (0.3%) were also diagnosed with a lymphoid neoplasm during their lifetime (23 from the MPN database and 11 from the CLL database). A similar percentage of patients were diagnosed with the LPN either before (47%) or after (44%) the MPN diagnosis. LPN was diagnosed most often in patients with MF ($n = 14$; 4%), and NHL was the most common lymphoid malignancy ($n = 17$; 50%). Demographic and clinicobiological characteristics of all patients at the time of presentation to our institution are summarized in Table 1, and detailed information about patients' treatment and clinical outcome are included in Table 2. Male to female ratio was 1.4:1, and the median age at diagnosis for each disease (LPN or MPN) was the same (56 years). The median follow-up time from the date of MPN diagnosis was longer than the median follow-up time from presentation to our institution (84 vs 37 months, respectively). When divided by MPN subtype or timing of LPN diagnosis, demographic (gender, age), clinical characteristics (JAK2, karyotype, PS, splenomegaly) and primary therapeutic interventions were similar. The only significant clinical differences were that 100% of PV patients harbored the JAK2 V617F mutation, and symptomatic splenomegaly was more common in patients with MF. Most of the patients with NHL had an aggressive histology (70%) and more than half of them presented with an advanced stage of their disease, whereas the majority of CLLs, HLs and multiple myeloma cases presented in the early stages.

The majority of patients received treatment for their first disease, whether MPN or LPN (73 vs 94%), with monotherapy being the most common. Detailed data are shown in Table 2 and summarized