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Secondary solid tumors and lymphoma in patients with essential thrombocythemia and polycythemia vera – single center experience

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Essential thrombocythemia (ET) and polycythemia vera (PV) are chronic myeloproliferative neoplasms (MPNs) with increased risk of thrombosis, and evolution to myelofibrosis or acute myeloid leukemia [1]. Some of the therapeutic agents commonly used as therapy for ET and PV, such as alkylating agents, pipobroman, and radioactive phosphorus, have been associated with an increased risk of leukemic transformation [1, 2, 3]. In recent years, several large population based studies conducted in Italy [4], Denmark [5] or Sweden [6] have shown an increased risk of developing a secondary solid tumor or lymphoid malignancy in patients with ET and PV in comparison to the general population. Whether the therapy these patients received had a role in the development of these secondary malignancies is not clear.

Herein, we present the findings of a retrospective study of all patients with ET and PV evaluated at MD Anderson Cancer Center between 1960 and 2014. We measured the prevalence of secondary malignancies in these patients and their possible association with the treatment received. Of 445 patients with a confirmed diagnosis of ET or PV, 27 were excluded from the analysis because they were lost to follow-up after the first visit. Among the remaining 417 patients (4,063 person-years), 168 were diagnosed with ET and 249 with PV, with a female:male ratio of 1.4:1. We identified 32 patients who developed a secondary malignancy (24 non-hematologic and 8 hematologic), excluding all types of leukemia, carcinomas in situ, superficial bladder carcinoma, and non-melanoma skin cancers. The results are summarized in Table 1. The cumulative incidence of second malignancy was 7.7% (person/years of follow up = 8 person per 1000 years). Although the calculated standardized incidence ratios (SIRs) were suggestive of an increased probability of developing SM among patients with ET/PV as compared to general US population (e.g. for melanoma, thyroid carcinoma, sarcomas, NHL), the only statistically significant results were seen for NHL, likely because fewer than 5 cases were observed in the other SM types. SIR calculations are shown in Suppl. Tables 1 & 2. The median follow up from ET/PV diagnosis was 108 months and median follow up from presentation to our institution was 69 months: 44% of patients were followed for more than 10 years from initial diagnosis. The median time from diagnosis of ET or PV to diagnosis of a secondary malignancy was 82 months and

was shorter for non-hematologic secondary malignancies than for hematologic secondary malignancies (62 months vs 128 months, respectively). No statistically significant differences in demographics or clinical characteristics were noted between patients with and without secondary malignancies (Supplemental Table 3). However, we observed statistically significant differences in clinical characteristics between treated and non-treated patients (Supplemental Table 4). Among 358 patients (85.6%) who received cytotoxic therapy for their ET/PV, 53% have received more than one myelosuppressive drug during follow-up, with hydroxyurea in combination with various other agents used most often (180 patients), followed by anagrelide (140 patients) and interferon (89 patients). Alkylating agents were used in 31 patients [busulfan in 12, thiotepa in 5]. All patients treated with alkylating agents were also treated with hydroxyurea, anagrelide or interferon (either before or after treatment with the alkylating agent). Surprisingly, we observed a significantly higher number of secondary malignancies in patients who had received no prior therapy (17%), as compared with patients who received monotherapy (9.6%) or multiple therapies (4%) (chi-square value = 11.952, p=0.003). However, this finding should be taken with caution. The results could be biased by the character of our institution, which is a referral center, and therefore by patient selection. For example, secondary malignancies were noted in 9 patients treated with hydroxyurea; however, these patients were older, and the secondary cancers occurred after a relatively short time on treatment (median, 3 years). In addition, many of them had other existing cancer-risk factors, such as a prolonged (20+ years) smoking history in all patients diagnosed with lung carcinoma or colonic polyposis in the patient diagnosed with colorectal carcinoma. The retrospective nature of our analysis does not permit us to reach definitive conclusions regarding the overall risk of developing secondary malignancies in patients with ET and PV in relation to type of therapy received.

In summary, our results appear to support previously published findings [2] that secondary malignancies occur in patients with ET and PV regardless of treatment received.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

[PART I. + II.] Main characteristics of all patients (n=417), according to treatment received (PART I.) and its association with observed SM (PART II.)

PART I.					
Treatment type	**Patients, n (%)**	**males n (%)**	**Age median, (range), mos**	**Total treatment length[d] median, [range], mos**	**Total follow up time median, [range], mos**
Monotherapy	**136 (33)**	**57 (42)**	**49 (20–80)**	**60 (2–240)**	**95 (5.8–362)**
Hydrea	73 (53.7)	34	67 (37–80)	60 (6–216)	73 (9.2–285)
Anagrelide	14 (10.3)	3	49 (25–78)	78 (2–144)	113 (9.9–297.4)
Interferon	42 (31)	12	45.5 (20–69)	72 (2–240)	98 (9.6–285)
Others[a]	7 (5)	6	44 (23–67)	72 (24–108)	144 (47.5–362)
Multiple treatments	**222 (53)**	**83 (37)**	**51 (15–84)**	**108 (2–360)**	**126 (0.2–340)**
2 lines[b]	172 (77.5)	63	52 (15–84)	96 (2–324)	123 (15.5–174)
3 and more lines[c]	50 (22.5)	20	49 (16–72)	132 (3–360)	157 (7.7–474)
No treatment	**59 (14)**	**24 (42)**	**48 (15–83)**	**NA**	**53.6 [0.2–314]**
PART II.					
			Monotherapy, type, (n)	**Multiple treatments, (n)**	**No treatment, (n)**
SM type, number according to treatment	B-NHL	DLBCL	HU (1)	2 lines (2)	
		BL		3 lines (1)	
		MCL		3 lines (1)	(1)
		MALT			(1)
	T-NHL				(1)
	GI tract	CRC	HU (1), INF (1)	2 lines (1)	
		Cholangio	OTH (1)		
	GYN (female)	Breast	ANAGR (2)	2 lines (1)	(1)
		SCC vulva			(1)
	GU tract	Prostate	HU (1)		(1)
		Bladder		2 lines (1)	

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PART I.					
Treatment type	**Patients, n (%)**	**males n (%)**	**Age median, (range), mos**	**Total treatment length[d] median, [range], mos**	**Total follow up time median, [range], mos**
		RCC		2 lines (1)	
	Lung	NSCLC	HU (2)		
		SCLC	HU (1)		
	Melanoma		HU (2)		(1)
	Thyroid Ca				(2)
	Sacroma	NFS			(1)
		STS		2 lines (1)	
	NET		HU (1)		
SM, n (%)	Total		13 (9.6)	9 (4)	10 (17)
	HU: ANAGR: INF: OTH		9 (12): 2 (14): 1 (2.4): 1 (14)		
	2 lines: 3 lines			7 (4): 2 (5)	
Males with SM, n, (%)	Total		6 (46)	4 (45)	7 (70)
	HU: OTH		5 (83) 1 (100)		
	2 lines: 3 lines			2 (29): 2 (100)	
Time from MPN dx to SM median, [range], mos	Total		62 [5–215]	85 [14.5–128]	73 [0.1–251]
	HU: ANAGR: INF: OTH		49.5 [5–125]: 154 [140–168]: 62: 90.4		
	2 lines: 3 lines			85 [15–128]: 110 [79–141]	
Treatment length before SM, median, [range], mos	Total		42 [2–216]	26 [2–360]	NA
	HU: ANAGR: INF:OTH		36 [2–216]: 2 [2–2]: 48: 72		
	2 lines: 3 lines			24 [24–96]: 105 [72–138]	

Abbr.: HU=hydroxyurea, ANAGR= Anagrelide, INF= Interferon, OTH= Others, SM=secondary malignancy, DLBCL= Diffuse large cell lymphoma, MCL = Mantle cell lymphoma, MALT = Mucosa associated lymphoid tumor, BL = Burkitt lymphoma, CRC = Colorectal carcinoma, NET = Neuroendocrine carcinoma, NSCLC = Non-small cell lung carcinoma, SCLC = Small cell lung carcinoma, STS = Soft tissue sarcoma, RCC = Renal cell carcinoma, NFS = Neurofibrosarcoma, SCC = Squamous cell carcinoma

[a] Imatinib (n=4), busulfan (n=2), 6-mercaptopurine (n=1)

[b] Hydroxyurea + Anagrelide (n=85), Hydroxyurea +Interferon (n= 35), Anagrelide + Interferon (n=13), Hydroxyurea with other agents (n=29);

[c] Hydroxyurea + Anagrelide + Interferon (n=20); all others (n=69)

[d] Treatment length was known in 217 patients