RESEARCH ARTICLE

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Secondary Solid Cancers in Patients with Philadelphia Chromosome-Negative Myeloproliferative Neoplasms: A Multicenter Study

Philadelphia-Negatif Miyeloproliferatif Neoplazili Hastalarda Sekonder Solid Kanser Gelişimi: Çok Merkezli Çalışma

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Abstract

Objective: We investigated the occurrence and characteristics of secondary solid cancers (SSCs) in patients with Philadelphia chromosome-negative myeloproliferative neoplasms (Ph- MPNs) from Türkiye. We identified the potential risk factors for SSC development, including the impact of cytoreductive therapies, and we assessed the influence of SSC on patient survival.

Materials and Methods: A total of 1013 Ph- MPN patients diagnosed between 1995 and 2022 were retrospectively analyzed. Data related to demographics, clinical and laboratory parameters, SSC development, cytoreductive therapy exposure, and survival outcomes were collected. Statistical analyses were performed using IBM SPSS Statistics 26.0.

Results: Of the analyzed Ph- MPN patients, 6.6% developed SSC, with carcinoma being the most common type. Older age at the time of Ph- MPN diagnosis and male sex were associated with SSC occurrence. Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no significant difference in complete blood count results, spleen size, Ph- MPN diagnostic groups, or driver mutation frequencies. However, patients with SSC had a higher frequency of arterial thrombosis and a tendency towards an increased rate of total thrombosis (p=0.030 and p=0.069, respectively). In multivariate analysis, arterial thrombosis was the sole independent risk factor and interferon (IFN)-based therapy was the sole protective factor for SSC development. Median overall survival (OS) did not differ between patients with and without SSC except for polycythemia vera patients with SSC, who had shorter OS (175±15 versus 321±26 months, respectively; p=0.005).

Conclusion: This study highlights the prevalence and characteristics of SSCs in Turkish patients diagnosed with Ph- MPNs. Arterial

Öz

Amaç: Türk popülasyonunda Philadelphia-negatif miyeloproliferatif neoplazi (Ph- MPN) hastalarında sekonder solid kanserlerin (SSK) sıklığının ve özelliklerinin araştırılması amaçlanmıştır. Sitoredüktif tedavinin etkisi de dahil olmak üzere SSK gelişiminde risk faktörlerinin tanımlaması ve SSK'nın hastanın sağkalımı üzerindeki etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntemler: 1995-2022 yılları arasında tanı alan 1013 Ph- MPN hastası retrospektif olarak analiz edilmiştir. Demografik özellikler, klinik ve laboratuvar parametreleri, SSK gelişimi, sitoredüktif tedaviye maruz kalma ve sağkalım ile ilgili veriler toplanmıştır. İstatistiksel analizler IBM SPSS Statistics 26,0 yazılımı kullanılarak yapılmıştır.

Bulgular: Ph- MPN hastalarının %6,6'sında SSK gelişmiştir ve en sık görülen tip karsinomdur. Ph- MPN tanısında ileri yaş ve erkek cinsiyet SSK gelişimiyle ilişkili bulunmuştur. SSK olan ve olmayan hastalarda kan sayımı, dalak boyutu, Ph- MPN tanı grupları ve somatik mutasyon sıklığı açısından anlamlı farklılık görülmemiştir. SSK gelişen hastalarda arteriyel tromboz sıklığı daha yüksek olmakla beraber total tromboz sıklığında artış eğilimi bulunmuştur (sırasıyla p=0,030, p=0,069). Çok değişkenli analizde, SSK gelişimi için arteriyel tromboz tek bağımsız risk faktörü ve interferon (IFN) bazlı tedavi tek koruyucu faktör olarak bulunmuştur. SSK gelişen ve gelişmeyen hastalar arasında ortanca sağkalım (OS) benzer bulunmuştur. PV'de SSK gelişen hastalarda gelişmeyenlere göre OS daha kısa bulunmuştur (sırasıyla 175±15 ve 321±26 ay; p=0,005).

Sonuç: Çalışmamız Ph- MPN tanısı alan Türk hastalarda SSK'nın prevalansını ve özelliklerini yansıtmaktadır. Arteriyel tromboz artmış SSK riski ile ilişkili bulunmakla beraber IFN bazlı tedavi SSK'ya potansiyel koruyucu etki göstermiştir. Arteriyel trombozu olan Ph-

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Abstract

thrombosis was associated with increased SSC risk while IFN-based therapy offered potential protection from SSC. Screening for SSC in Ph- MPN patients with arterial thrombosis may be valuable. These findings emphasize the importance of malignancy screening in Ph- MPN patients, especially in high-risk subgroups, and call for further research to elucidate the underlying mechanisms and optimize treatment strategies.

Keywords: Philadelphia chromosome-negative myeloproliferative neoplasm, Secondary solid cancers, Cytoreductive treatment, Interferon

Öz

MPN hastalarında SSK taraması yapılması uygun olabilir Bu bulgular Ph- MPN hastalarında, özellikle de yüksek riskli grupta malignite taramasının önemini ve altta yatan mekanizmaların aydınlatılması ve tedavi stratejilerinin optimize edilmesi için daha fazla araştırma yapılmasının önemini vurgulamaktadır

Anahtar Sözcükler: Philadelphia-negatif kronik miyeloproliferatif neoplazi, Sekonder solid kanser, Sitoredüktif tedavi, İnterferon

Introduction

Philadelphia chromosome-negative myeloproliferative neoplasms (Ph- MPNs) are characterized by the overproduction of differentiated cells, clonal myeloproliferation, and somatic mutations in *JAK2*, *CALR*, *MPL*, or other subclones [1,2,3]. Polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF) are classified as Ph- MPNs [4]. Major complications of Ph- MPNs are thrombosis, bleeding, and transformation to myelofibrosis, acute myeloid leukemia, and myelodysplastic syndrome [5]. One important concern in the course of Ph- MPNs is the risk of development of solid cancers. Some studies have reported an increased risk of secondary solid cancers (SSCs) in cases of Ph- MPNs while others have found no relationship between Ph- MPNs and SSCs in comparison to population-based cohorts [6,7,8,9,10]. The proposed mechanisms accountable for the increased SSC risk include the presence of shared genetic risk factors, an inherent tendency to develop cancer, the impact of antineoplastic agents, and possible links with chronic inflammation or immune dysfunction [11,12,13,14].

Using data from a large cohort of Turkish Ph- MPN patients, we aimed to determine the types and frequencies of SSCs, identify the risk factors for SSCs including the role of cytoreductive therapies, and evaluate the impact of SSCs on survival in patients with Ph- MPNs.

Materials and Methods

Patients

A cohort of 1013 patients diagnosed with Ph- MPNs from 1995 and 2022 and under follow-up in the adult hematology sections of University of Health Sciences İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital and the İstanbul University Medical Faculty were included. All selected Ph- MPN patients fulfilled the 2016 World Health Organization diagnostic criteria. In this retrospective descriptive study, data on demographic characteristics, laboratory and clinical parameters at the time of diagnosis, mutation status (*JAK2*V617F, *MPL*, and *CALR*), SSC development during follow-up and date of diagnosis of the SSC, death, presence of a history of thrombosis regardless of Ph- MPN diagnosis, overall survival (OS), and malignancy-free survival (MFS) were collected from patient reports and electronic medical records. Triple-negative MPN patients were defined as ET or PMF patients who did not display the *JAK2*, *MPL*, or *CALR* driver mutations.

Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (study number: 2021-18-14, date: 20.09.2021).

Statistical Analysis

Statistical analysis was performed using IBM SPSS Statistics 26.0 (IBM Corp., Armonk, NY, USA). Kolmogorov-Smirnov and Shapiro-Wilk tests were used to confirm that the data were normally distributed. Median (minimum-maximum) values were given for data not normally distributed and mean ± standard deviation values were given for data with normal distribution. Categorical variables were expressed as numbers of cases and percentages. Cross-table statistics with the Pearson chi-square test and Fisher exact test were used to compare categorical variables between the groups. Quantitative data not normally distributed were evaluated with the Mann-Whitney U and Kruskal-Wallis tests. Multivariate analysis was performed using the Cox proportional hazards regression model. Estimations of OS and MFS in cases of PV, ET, and PMF were performed by Kaplan-Meier analysis. For all hypotheses tested, two-tailed p values of <0.05 were considered statistically significant.

Results

Characteristics of Ph- MPN Patients

Our study group included a total of 1013 Ph- MPN patients with a mean follow-up period of 91.565.1± months. The patients' clinical features are outlined in Table 1. The frequencies of diagnosis of ET, PV, and PMF were 41.4%, 37.5%, and 21.1%, respectively. The median age at Ph- MPN diagnosis was 54 (range: 12-88) years. The median age of the ET patients was

Table 1. Clinical features of the patients.

	MPN (n=1013)	PV (n=380)	ET (n=419)	PMF (n=214)	p**	PV vs. ET*	PV vs. PMF*	ET vs. PMF*
Sex **Female, n (%)** **Male, n (%)**	 497 (49.1%) 516 (50.9%)	 122 (32.1%) 258 (67.9%)	 266 (63.5%) 153 (36.5%)	 109 (50.9%) 105 (49.1%)	**<0.001**	**<0.001**	**<0.001**	**0.002**
Age in years at MPN diagnosis, median (range) **<65, n (%)** **≥65, n (%)**	54 (12-88) 736 (72.7%) 277 (27.3%)	55 (17-84) 284 (74.7%) 96 (25.3%)	51 (12-88) 312 (74.5%) 107 (25.5%)	57.5 (21-84) 140 (65.4%) 74 (34.6%)	**<0.001** **0.028**	**0.029** 0.926	**0.008** **0.016**	**<0.001** **0.017**
***JAK2*V617F, n (%)**	730 (72.1%)	305 (80.3%)	269 (64.2%)	156 (72.9%)	<0.001	<0.001	0.039	0.019
***CALR*, n (%)**	71 (7%)	-	58 (13.8%)	13 (6.1%)	-	-	-	0.003
***MPL*, n (%)**	4 (0.4%)	-	3 (0.7%)	1 (0.4%)	-	-	-	1.000
Triple-negative, n (%)	136 (13.4%)	-	90 (21.5%)	46 (21.5%)	-	-	-	0.996
WBC at MPN diagnosis, median (range)	10,400 (2300-94,000)	10795 (2510-34,300)	9900 (4200-51,400)	11,350 (2300-94,000)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Hb at MPN diagnosis, median (range)	14.7 (5.5-24.5)	17.8 (11.4-24.5)	13.6 (6.7-17.1)	11.4 (5.5-19.5)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
HCT at MPN diagnosis, median (range)	44.5 (14-85)	54 (36-85)	41 (21-55.5)	35.4 (14-62.7)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
PLT at MPN diagnosis, median (range)	636,000 (28,000-2,786,000)	(40,600-1,818,000)	853,000 (110,000-2,786,000)	425,500 (28,000-2,309,000)	**<0.001**	**<0.001**	0.204	**<0.001**
Spleen size at MPN diagnosis, median (range)	120 (70-340)	120 (87-260)	120 (75-301)	178 (70-340)	**<0.001**	0.113	**<0.001**	**<0.001**
CV risk, n (%)	716 (70.7%)	300 (78.9%)	278 (66.3%)	138 (64.5%)	**<0.001**	**<0.001**	**<0.001**	**0.640**
Thrombosis, n (%) **Arterial, n (%)** **Venous, n (%)**	356 (35.1%) 264 (25.1%) 92 (12.3%)	144 (37.9%) 110 (28.9%) 42 (11.1%)	138 (32.9%) 107 (25.2%) 48 (11.5%)	74 (34.6%) 47 (22%) 34 (15.9%)	0.335 0.168 0.184	0.143 0.279 0.857	0.421 0.064 0.090	0.678 0.321 0.116
Cytoreductive therapy, n (%) **Hydroxyurea, n (%)** **IFN, n (%)** **RUX, n (%)**	871 (86%) 831 (82%) 94 (9.3%) 95 (9.4%)	314 (82.6%) 311 (81.8%) 16 (4.2%) 15 (3.9%)	355 (84.7%) 327 (78%) 59 (14.1%) 5 (1.2%)	202 (94.4%) 193 (90.2%) 19 (8.9%) 75 (35%)	**<0.001** **<0.001** **<0.001** **<0.001**	0.425 0.181 **<0.001**	**<0.001** **0.006** **0.02** **<0.001**	**<0.001** **<0.001** 0.06 **<0.001**
Secondary solid cancer, n (%)	67 (6.6%)	31 (8.4%)	26 (6.2%)	10 (4.7%)	0.236	0.284	0.108	0.431

MPN: Myeloproliferative neoplasm; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; WBC: white blood cell count; Hb: hemoglobin; HCT: hematocrit; PLT: platelet count; CV: cardiovascular; IFN: interferon; RUX: ruxolitinib.

lower than that of PV and PMF patients (51, 55, and 57.5 years, respectively; p<0.001).

Sixty-seven patients (6.6%) developed SSCs. Among those 67 patients, there were 43 cases of carcinoma (64.2%), 16 cases of non-melanoma skin cancer (NMSC) (23.9%), 3 cases of sarcoma (4.5%), and 2 cases of melanoma (3%). In 9 patients, different types of SSC were diagnosed both prior to and after the diagnosis of Ph- MPN. Table 2 summarizes the occurrence of SSCs in our study group.

Comparative Analysis of Ph- MPN Patients with Secondary Solid Cancers

The mean time to SSC occurrence was 80.03±60.5 months. PV, ET, and PMF patients showed no significant differences in median time to SSC occurrence (p>0.05). The median age at Ph- MPN diagnosis was significantly higher for patients diagnosed with SSC compared to patients with no diagnosis of SSC (63 [37-78] versus 54 [12-88] years, respectively; p<0.001). The frequency of patients aged ≥65 years among the patients diagnosed with SSC was higher compared to patients with no diagnosis of SSC (44.8% versus 26.1%, respectively; p=0.001). Men constituted 64.2% (n=43) and 50% (n=473) of patients diagnosed with SCC and patients without a diagnosis of SCC, respectively. The frequency of male patients was significantly higher among patients with SSCs (p=0.025). Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no significant difference in leukocyte count, hemoglobin and hematocrit levels, platelet count, spleen size, Ph- MPN diagnostic subgroups, frequencies of driver mutations, and follow-up period (p>0.05 for all) (Table 3). There was a trend towards increased incidence of total thrombosis in Ph- MPN patients diagnosed with SSC compared to patients with no diagnosis of SSC (44.8% versus 34.5%, respectively; p=0.069). The frequency of arterial thrombosis in Ph- MPN patients diagnosed with SSC was statistically significantly higher compared to patients with no diagnosis of SSC (37.3% versus 25.3%, respectively; p=0.030).

Table 2. Occurrence of secondary solid cancers in the study group.

Solid cancer subtype after MPN diagnosis	n (%)
Basal cell carcinoma	11 (16.4%)
Breast	8 (11.9%)
Prostate	8 (11.9%)
Lung	6 (9.0%)
Blader	5 (7.5%)
Endocrine	4 (6%)
Colorectal	4 (6.0%)
Kidney	3 (4.5%)
Stomach	3 (4.5%)
Squamous cell carcinoma	3 (4.5%)
BCC and SCC	2 (3.0%)
Melanoma	2 (3.0%)
Liver	1 (1.5%)
Mesothelioma	1 (1.5%)
Liposarcoma	1 (1.5%)
Ovarian	1 (1.5%)
Head-neck	1 (1.5%)
BCC and lung	1 (1.5%)
BCC and kidney	1 (1.5%)
Lung and bladder	1 (1.5%)
Total	**67 (100%)**

BCC: Basal cell carcinoma; SCC: squamous cell carcinoma.

The clinical characteristics of Ph- MPN patients with SSCs stratified by diagnostic subgroups are summarized in Table 4.

Cytoreductive Therapy Exposure

Eight of 141 (5.7%) Ph- MPN patients not exposed to cytoreductive treatment developed SSC while 8 of 67 Ph- MPN patients diagnosed with SSC had no history of cytoreductive treatment. Regardless of whether hydroxyurea (HU) exposure occurred as a single line of cytoreductive treatment or as a part of multiple lines of cytoreductive treatment, the rate of SSC among patients exposed to HU was 7%. The rates of SSC among Ph- MPN patients exposed to ruxolitinib (RUX), anagrelide, and interferon (IFN)-based therapy were 5.3%, 4%, and 2.1%, respectively. A trend towards a decrease in SSC development was observed with IFN treatment compared to the non-IFN group (2.7% versus 9.7%, respectively; p=0.066) (Table 3).

For Ph- MPN patients under cytoreductive treatment, the impact of first- and second-line treatments on the development of SSC was examined. The rate of SSC was significantly higher in patients with exposure to HU as first-line monotherapy compared to patients with exposure to HU as a part of multiple lines of cytoreductive treatment and patients without exposure to HU (7.8% and 4.6%, respectively; p=0.046) (Table 3).

The impact of cytoreductive treatment options on the subtype of SSC diagnosed was examined. It was determined that 63.8% of SSCs diagnosed in patients exposed to HU were carcinomas, 25.9% were NMSC, and 3.4% were concomitant carcinoma and NMSC. The difference in the rates of the aforementioned SSC subtypes diagnosed was not significant (p>0.05). There was no significant difference in SSC subtypes diagnosed in patients exposed to anagrelide or IFN-based therapy. Five patients with RUX exposure developed SSCs, all of which were NMSC, while 11 of 62 (17.7%) Ph- MPN patients without exposure to RUX developed SSCs (p=0.009). All 5 patients who were exposed to RUX and developed SSCs had a previous history of HU exposure

Table 3. Comparison of clinical characteristics of patients with and without secondary solid cancer.

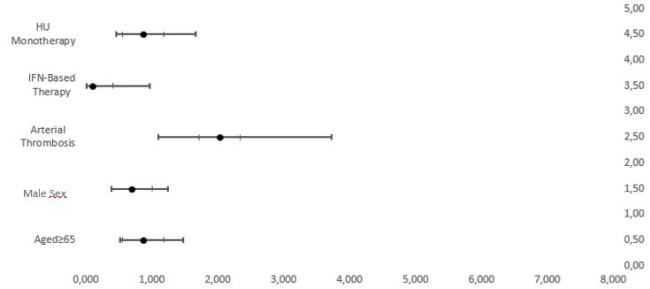
	SSC (n=67)	No SSC (n=946)	p
Sex **Female, n (%)** **Male, n (%)**	 24 (35.8%) 43 (64.2%)	 473 (50.0%) 473 (50.0%)	 **0.025**
Age in years at MPN diagnosis, median (range) **<65, n (%)** **≥65, n (%)**	63 (37-78) 24 (35.8%) 43 (64.2%)	54 (12-88) 24 (35.8%) 43 (64.2%)	**<0.001** **0.001**
WBC at MPN diagnosis, median (range)	10,160 (3900-57,260)	10,400 (2300-94,000)	0.457
Hb at MPN diagnosis, median (range)	15.6 (5.8-21)	14.6 (5.5-24.5)	0.734
HCT at MPN diagnosis, median (range)	45.12 (19-69.5)	44.40 (14-85)	0.882
PLT at MPN diagnosis, median (range)	621,000 (80,000-2,786,000)	645,500 (28,000-2,631,000)	0.803
Spleen size at MPN diagnosis, median (range)	120 (102-320)	120 (70-340)	0.658
Diagnostic group **PV, n (%)** **ET, n (%)** **PMF, n (%)**	 31 (46.2%) 26 (38.8%) 10 (14.9%)	 349 (36.9%) 393 (41.5%) 204 (21.6%)	 0.236
Driver mutation ***JAK*, n (%)** ***CALR*, n (%)** ***MPL*, n (%)** **Triple-negative, n (%)**	 49 (73.1%) 7 (10.4%) 1 (1.6%) 10 (14.9%)	 681 (84.9%) 65 (8.1%) 3 (0.4%) 53 (6.6%)	 0.201
Thrombosis, n (%) **Arterial, n (%)** **Venous, n (%)**	30 (44.8%) 25 (37.3%) 6 (9.0%)	326 (34.5%) 239 (25.3%) 118 (12.5%)	0.069 0.03 0.396
Cytoreductive therapy **No cytoreductive therapy** **HU therapy** **Single-drug HU exposure (first-line monotherapy)** **IFN therapy** **Single-drug IFN exposure (first-line monotherapy)** **RUX** **Single-drug RUX exposure (first-line monotherapy)** **Anagrelide** **Single-drug anagrelide exposure (first-line monotherapy)**	 8 (11.9%) 58 (86.6%) 49 (73.1%) 2 (2.9%) 1 (1.45%) 5 (7.5%) 0 (0.0%) 4 (5.9%) 0 (0.0%)	 133 (14%) 773 (81.7%) 576 (60.8%) 92 (9.7%) 21 (2.2%) 90 (9.5%) 7 (0.73%) 96 (10.1%) 4 (0.4%)	 0.628 0.317 **0.046** **0.066** 1.000 0.578 1.000 0.268 1.000

SSC: Secondary solid cancer; MPN: myeloproliferative neoplasm; WBC: white blood cell count; Hb: hemoglobin; HCT: hematocrit; PLT: platelet count; PV: polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; HU: hydroxyurea; IFN: interferon; RUX: ruxolitinib.

and 1 of those 5 patients had a previous history of exposure to anagrelide. Of the 18 Ph- MPN patients who developed NMSC, 17 had been exposed to HU.

Multivariate Analysis

We performed Cox regression analysis to investigate the impact of patient age of ≥65 years, male sex, arterial thrombosis, HU as first-line monotherapy, and IFN-based therapy on the time to development of SSC. After adjustment for confounding variables, the occurrence of arterial thrombosis remained independently associated with the risk of SSC (odds ratio [OR]: 2.024; 95% confidence interval [CI]: 1.100 to 3.724; p=0.023). SSC was independently prevented by IFN-based therapy (OR: 0.101; 95% CI: 0.11 to 0.967; p=0.047) (Figure 1). In multivariate analysis, patient age of ≥65 years, male sex, and HU as first-line monotherapy lost their significance for the time to development of SSC.



	Odds Ratio (95% CI)	p value
HU Monotherapy	0.868 (0.453-1.662)	0.668
IFN-Based Therapy	0.101 (0.011-0.967)	0.047
Arterial Thrombosis	2.024 (1.1-3.724)	0.023
Male Sex	0.698 (0.392-1.243)	0.222
Aged≥65	0.869 (0.513-1.472)	0.601

Figure 1. Multivariate Cox regression analysis of factors contributing to the development of secondary solid cancers.
HU: Hydroxyurea; IFN: interferon; CI: confidence ratio.

Table 4. Comparison of clinical characteristics of patients with secondary solid cancers stratified by diagnostic subgroups.

	PV (n=31)	ET (n=26)	PMF (n=10)	p**	PV vs. ET*	PV vs. PMF*	ET vs. PMF*
Sex							
Female, n (%)	9 (29.0%)	9 (34.6%)	6 (60.0%)	0.204	0.652	0.130	0.260
Male, n (%)	22 (71.0%)	17 (65.4%)	4 (40.0%)				
Age in years at MPN diagnosis, median (range)	62 (43-78)	64.5 (37-78)	59 (49-77)				
<65, n (%)	18 (58.1%)	13 (50.0%)	6 (60.0%)	0.932	0.724	0.952	0.804
≥65, n (%)	13 (41.9%)	13 (50.0%)	4 (40.0%)	0.786	0.543	1.000	0.717
WBC at MPN diagnosis, median (range)	9600 (3900-24,800)	9745 (5600-24,500)	14,100 (4200-57,260)	0.188	0.496	0.076	0.174
Hb at MPN diagnosis, median (range)	17.2 (13.5-21)	13.75 (6.7-16.5)	10.85 (5.8-16.1)	**<0.001**	**<0.001**	**<0.001**	**0.039**
HCT at MPN diagnosis, median (range)	51.6 (38.4-9.5)	40.7 (22-47)	32.3 (19-49)	**<0.001**	**<0.001**	**<0.001**	0.077
PLT at MPN diagnosis, median (range)	375,000 (93,000-1,246,000)	848,000 (453,000-2,786,000)	331,500 (80,000-1,267,000)	**<0.001**	**<0.001**	0.671	**0.005**
Spleen size (mm) at MPN diagnosis, median (range)	120 (110-200)	120 (114-180)	195 (102-320)	**<0.001**	0.306	**<0.001**	**<0.001**
Driver mutation							
***JAK*, n (%)**	24 (77.4%)	17 (65.4%)	8 (80.0%)				
***CALR*, n (%)**	.	5 (19.2%)	1 (10%)				
***MPL*, n (%)**	.	1 (3.8%)	-	0.516	0.314	1.000	0.688
Triple-negative, n (%)	.	3 (11.5%)	1 (10%)				
Thrombosis, n (%)	12	13	5 (50%)	0.436	0.156	0.455	0.652
Arterial, n (%)	10 (32.3%)	11 (42.3%)	4 (40.0%)	0.252	0.285	0.166	0.321
Venous, n (%)	3 (9.7%)	2 (7.7%)	1 (10.0%)	0.176	0.754	0.265	0.565
Cytoreductive therapy							
No cytoreductive therapy	5 (16.1%)	3 (11.5%)	-	0.464	0.715	0.310	0.545
Hydroxyurea	25 (80.6%)	23 (88.4%)	10 (100.0%)	0.277	0.422	0.307	0.262
Interferon	1 (3.2%)	1 (3.8%)	-	0.827	1.000	1.000	1.000
Ruxolitinib	-	-	5 (50.0%)	**0.001**	1.000	**0.009**	**<0.001**
Anagrelide	-	1 (3.8%)	3 (30.0%)	**0.002**	0.271	**0.011**	0.057

PV: Polycythemia vera; ET: essential thrombocythemia; PMF: primary myelofibrosis; MPN: myeloproliferative neoplasm; WBC: white blood cell count; Hb: hemoglobin; HCT: hematocrit; PLT: platelet count.

Median Survival and Malignancy-Free Survival

Median OS in patients diagnosed with SSC and in patients with no diagnosis of SSC were 273 months and 195 months, respectively (p>0.05). PV patients diagnosed with SSC had significantly worse median OS compared to PV patients with no diagnosis of SSC (175±15 months [95% CI: 144-206] versus 321±26 months [95% CI: 270-372], respectively; p=0.005). ET and PMF patients stratified by the status of SSC development showed no significant difference in OS. Mean MFS was 359.7 months (95% CI: 339-380) in the total cohort (Figure 2). There was no difference in MFS between PV and ET or PMF patients and the median MFS had not yet been reached.

Discussion

The most common types of cancer detected in our study population after exclusion of basal cell carcinoma were breast cancer, prostate cancer, and lung cancer. This finding is in accordance with the 2020 Global Cancer Observation Data database, which reports the aforementioned cancers as the three most common types of cancer in the general population, although the distribution frequencies and order are different for our Ph- MPN patients [15].

In the study conducted by Khanal et al. [16], which included PV patients, the frequency of SSC was higher in patients aged ≥60 years. Similarly, Brunner et al. [17] reported an increased risk of secondary cancer in Ph- MPN patients with advanced age. Consistent with previous data, the median age at the time of Ph- MPN diagnosis in our cohort was higher and the frequency of patients aged ≥65 years at diagnosis was also higher among patients diagnosed with SSC compared to the patients with no diagnosis of SSC. However, in multivariate analysis, patient age of ≥65 years showed no independent impact on

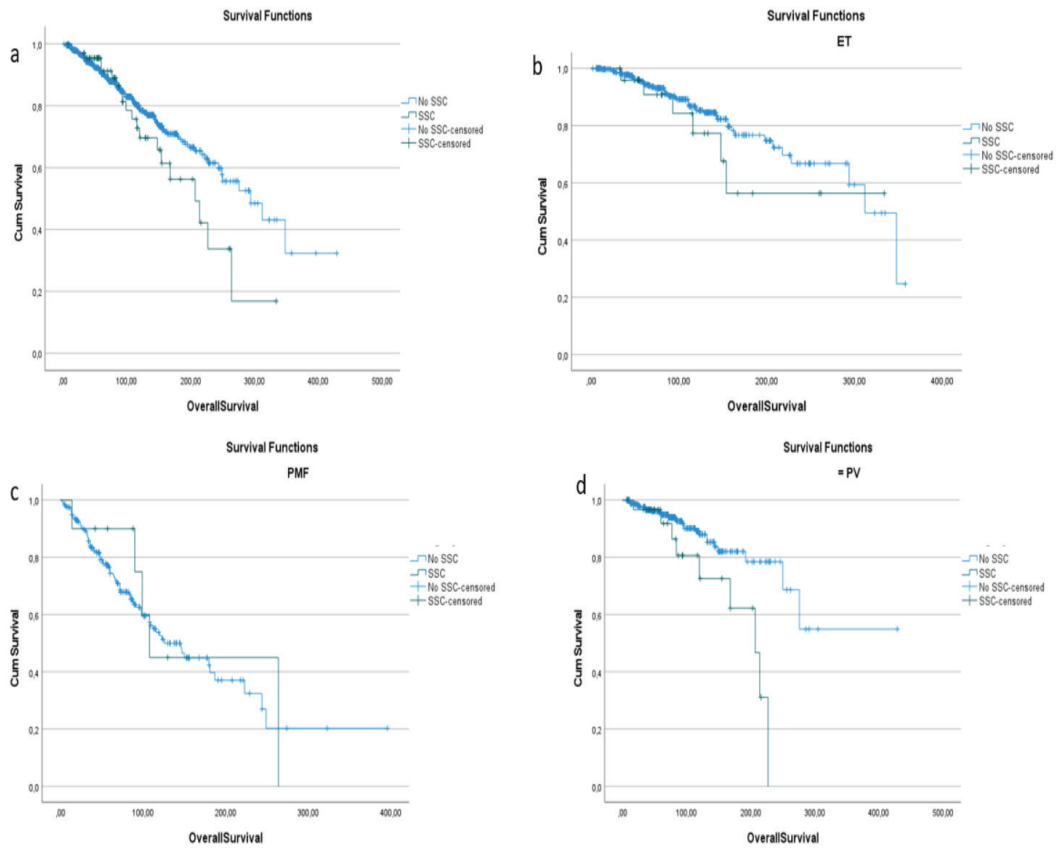


Figure 2. Median overall survival stratified by the development of secondary solid cancer (SSC): (a) entire patient cohort; (b) essential thrombocythemia (ET) patients; (c) primary myelofibrosis (PMF) patients; (d) polycythemia vera (PV) patients.

SSC diagnosis. Our observation was contrary to the findings by Zhang et al. [18], who identified patient age of ≥65 years as a risk factor for developing secondary cancer in MPN patients in their multivariate anal*ysis*.

Among Ph- MPN patients, a higher male frequency among SSC diagnoses was reported in some studies while others reported no difference in sex frequency [18,19]. In our study, the frequency of male patients was higher among patients diagnosed with SSC. However, no impact of sex on SSC development was observed in multivariate analysis. Zhang et al. [18] found no relationship between the *JAK2*V617F mutation and development of SSC. Similarly, in our study, Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC showed no difference for the frequency of triple-negative status or *JAK2*V617F, *CALR*, and *MPL* mutations. In line with our findings, Barbui et al. [20] reported no relationship between the aforementioned mutations and the diagnosis of SSC. Moreover, the incidence rates of PV, PMF, and ET were similar between our patients diagnosed with SSC and patients with no diagnosis of SSC.

The literature contains conflicting data about the relationship between secondary cancers and arterial thrombosis [18,20]. In the study by Barbui et al. [20], which included 647 Ph- MPN patients diagnosed with cancer and 1234 matched Ph- MPN patients without cancer diagnoses, the frequency of secondary cancers was higher among the Ph- MPN patients with arterial thrombosis [20]. However, the secondary cancers diagnosed in that study included both solid and hematological cancers. Zhang et al. [18] reported that arterial thrombosis after MPN diagnosis did not increase the risk of secondary solid or hematological cancers. Our study revealed a higher frequency of arterial thrombosis for patients diagnosed with SSC than patients with no diagnosis of SSC. In our multivariate analysis, arterial thrombosis emerged as a predictor of SSC. Chronic inflammation may be a common pathogenic mechanism between arterial thrombosis and secondary cancer in MPN patients [21,22]. In agreement with previous studies, the frequency of venous thrombosis was not different between our Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC [18,20].

The impact of HU therapy on secondary cancers in Ph- MPNs is still a matter of debate. Kissova et al. [23] reported a higher risk of SSC in patients treated with HU than patients treated with other cytoreductive therapies. In other studies that included Ph- MPN patients diagnosed with solid or hematologic cancers, a significant relationship between HU and SSC was not

demonstrated [18,20,24]. In our study, the frequency of SSC tended to be higher in patients on HU monotherapy compared to patients not exposed to HU. However, in multivariate analysis, we did not find HU monotherapy to be an independent risk factor for SSC. Our patients exposed to HU showed no significant difference for the subtypes of solid cancers diagnosed. In the cancer-specific multivariate analysis conducted by Barbui et al. [20], HU exposure was associated with a twofold higher risk of NMSC regardless of exposure to multiple lines of therapy or monotherapy. The contradictory result obtained in the study by Barbui et al. [20] may be attributed to their larger number of enrolled patients diagnosed with cancer.

Hansen et al. [25] demonstrated that the risk of developing solid cancer while receiving HU monotherapy was significantly higher than that for IFN. Furthermore, Hansen et al. [25] demonstrated that patients treated with HU had a tendency towards a higher risk of developing skin cancer while skin cancer developed in only one patient exposed to IFN. In our study, NMSC and malignant melanoma did not develop in patients exposed to IFN. Some other studies showed no association between IFN therapy and SSC risk [18,20]. The frequency of SSC diagnosis showed a tendency to be lower in our patients exposed to IFN-based therapy compared to non-exposed patients. Furthermore, a protective effect of IFN-based therapy against the development of SSC was demonstrated in Cox multivariate analysis.

Several previous studies demonstrated that the induction of molecular remission by early initiation of IFN, a drug with potential to reduce chronic inflammation and prohibit clonal expansion, reduces thrombohemorrhagic complications, myelofibrotic or leukemic transformation, and the rate of development of secondary cancers [13,26].

Barbui et al. [20] reported that the risk of secondary cancer in Ph- MPN patients exposed to RUX was almost fourfold higher compared to those not exposed to RUX and that the increased risk was limited to NMSC. We observed a significant relationship between RUX exposure and NMSC development. In our study, the 5 patients who developed solid cancer under RUX therapy were diagnosed with NMSC. However, all 5 patients were exposed to HU and 1 patient was exposed to anagrelide. Therefore, in our study, the relationship between RUX and the risk of NMSC is disputable.

To our knowledge, this is the first study focusing on the relationship between SSC and OS in Ph- MPN. In this study, there was no difference in OS between Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC. However, analysis across Ph- MPN subcategories demonstrated that PV patients diagnosed with SSC had significantly shorter OS. Some previous studies reported poor OS in Ph- MPN patients developing secondary cancers [8,18,27]. However, in contrast to our study population, the secondary cancers reported were not limited to SSCs but also included hematological malignancies. Differences in these Ph- MPN subgroup analyses should be confirmed by studies including larger numbers of patients.

Study Strengths and Limitations

The limitations of our study include its retrospective design and the lack of a cancer database providing a cumulative incidence for comparison against our cohort. Our Ph- MPN study population consisted of patients who presented to two centers between 1995 and 2022. Thus, it is not possible to compare our data with the cumulative cancer incidence in Türkiye. Another limitation is the lack of information regarding the duration and cumulative dose of cytoreductive therapy exposure. Thus, our findings may be insufficient to demonstrate a clear relationship between SSC and cytoreductive therapy. The strengths of our study are the recruitment of a larger Ph- MPN population than some previous studies; inclusion of PV, ET, and PMF patient subgroups, enabling separate analysis of SSC development in Ph- MPN subcategories; and a long follow-up period together with a multicenter study design.

Conclusion

The results of the present study have demonstrated that in a large series of Ph- MPN patients, the most common type of SSC diagnosed was carcinoma and that patients diagnosed with SSC were older at the time of diagnosis of Ph- MPN and were more frequently male. HU exposure as first-line monotherapy was associated with increased risk of SSC. However, in multivariate analysis including IFN-based therapy and arterial thrombosis, there was no significant impact of age of ≥65 years, male sex, or exposure to HU as first-line monotherapy on SSC risk. In patients diagnosed with SSC, there was a trend towards increased incidence of total thrombosis and a significant increase in the incidence of arterial thrombosis. The protective effect of INF-based therapy against SSC was of borderline significance but became significant when multivariate analysis was performed. RUX exposure was associated with a higher risk of NMSC compared to patients not exposed to RUX. In the entire cohort, there was no significant OS difference between Ph- MPN patients diagnosed with SSC and patients with no diagnosis of SSC. PV patients diagnosed with SSC had a significantly worse median OS compared to PV patients with no diagnosis of SSC.

Our study contributes to the literature by providing the first analysis of the relationship between Ph- MPN and malignancies limited to solid cancers in a relatively large patient population. For Ph- MPN, malignancy screening seems to gain importance in patients with arterial thrombosis. Further studies are needed to determine whether MPN patients are predisposed to SSC regardless of the use of cytoreductive therapy, to determine whether the duration and cumulative dose of cytoreductive

therapy exposure have an impact on SSC occurrence, to elucidate the role of HU or RUX in increasing the risk of SSC in MPNs, to confirm the potential protective effect of IFN against SSC, and to identify other factors that may lead to the emergence of SSC. Our data need to be confirmed with further studies enrolling more patients.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the Local Ethics Committee of University of Health Sciences İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital (study number: 2021-18-14, date: 20.09.2021).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Concept: F.H.; Design: F.H., İ.Y.H.; Data Collection or Processing: Ö.N.A., E.A.; Analysis or Interpretation: Ö.N.A., E.G.; Literature Search: Ö.N.A, A.D.A., E.G., M.N.; Writing: F.H., İ.Y.H., E.A.

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