RESEARCH ARTICLE

Gaziantep Medical Journal 2016;22(2):72-75 • DOI: 10.5578/GMJ.32154

Second malignancies in Philadelphia-positive and -negative myeloproliferative neoplasms: A single center study

Philadelphia-pozitif ve Philadelphia-negatif myeloproliferatif neoplazmlarda ikincil kanserler: Tek merkez çalışması

Soner SOLMAZ[1], Aslı KORUR[2], Çiğdem GEREKLİOĞLU[2], Süheyl ASMA[2], Nurhilal BÜYÜKKURT[1], Mutlu KASAR[1], Mahmut YERAL[1], İlknur KOZANOĞLU[3], Can BOĞA[1], Hakan ÖZDOĞU[1]

[1] Clinic of Hematology, Başkent University Adana Hospital, Adana, Turkey

[2] Clinic of Family Medicine, Başkent University Adana Hospital, Adana, Turkey

[3] Clinic of Hematology Research Laboratory, Başkent University Adana Hospital, Adana, Turkey

ABSTRACT

Introduction: Leukemic transformation (LT) of both Philadelphia (Ph) -positive and -negative myeloprolifetarive neoplasms (MPNs) is a well-known subject. However sufficient data are not available in literature from Turkey about the frequency of second malignancies (SMs) except LT in patients with MPNs. In this study, it was aimed to investigate the frequency of SMs in Ph-positive or -negative MPN cases.

Materials and Methods: A total of 438 patients diagnosed with classical MPN according to WHO 2008 diagnostic criteria were included in the study.

Results: SMs were detected in 15 out of 438 patients (3.4%). In this study, cancer incidence rate was found higher (1149.8/100.000 person-years for males and 540.8/100.000 person-years for females with MPNs) compared with Turkey data.

Conclusion: SM frequency is significantly higher than normal population in patients with MPNs. Therefore these patients should be carefully examined for SM symptoms and signs.

Keywords: *Myeloproliferative neoplasms, chronic myeloid leukemia, second malignancy*

ÖZ

Giriş: Philadelphia-pozitif ve Philadelphia-negatif myeloproliferatif neoplazmların (MPN) lösemik transformasyonu (LT) iyi bilinen bir konudur. Bununla birlikte literatürde MPN'li hastalarda LT dışı ikincil kanser sıklığı hakkında ülkemizden yeteri kadar veri bulunmamaktadır. Bu çalışmada, Philadelphia-pozitif ve Philadelphia-negatif MPN tanılı hastalarda ikincil kanser sıklığının araştırılması amaçlanmıştır.

Materyal ve Metod: Dünya Sağlık Örgütü 2008 tanı kriterlerine göre klasik MPN tanısı alan 438 hasta bu çalışmaya dahil edilmiştir.

Bulgular: Çalışmada 438 hastanın 15 (%3.4)'inde ikincil kanserler tespit edilmiştir. Türkiye verisiyle kıyaslandığında kanser insidans hızı yüksek bulunmuştur (erkeklerde 1149.8/100.000 kişi-yıl, kadınlarda 540.8/100.000 kişi-yıl).

Sonuç: İkincil kanser sıklığı MPN tanılı hastalarda genel popülasyona kıyasla belirgin olarak daha yüksektir. Bu nedenle bu hastalar ikincil kanser belirti ve bulguları açısından dikkatlice değerlendirilmelidir.

Anahtar Kelimeler: *Myeloproliferatif neoplazmlar, kronik myeloid lösemi, ikincil kanser*

Yazışma Adresi/Correspondence: Soner SOLMAZ

Başkent Üniversitesi Adana Hastanesi, Hematoloji Kliniği, Adana, Türkiye

Telefon/Tel: *+90 322 3272727* • ***E-posta/E-mail:*** *drssolmaz@gmail.com*

Geliş Tarihi/Received: 25.01.2016 • **Kabul Ediliş Tarihi/Accepted:** 12.03.2016

INTRODUCTION

Myeloproliferative neoplasms (MPNs), formerly referred to as chronic myeloproliferative disorders, are a class of stem cell-derived myeloid hematological malignancies(1). MPNs are characterized by expansion of one or more hematopoietic cell lineages with resulting bone marrow hypercellularity (1). The World Health Organization (WHO) classification system for hematological malignancies includes eight clinico-pathological entities under the category of MPNs: chronic myelogenous leukemia (CML), polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), chronic neutrophilic leukemia (CNL), chronic eosinophilic leukemia-not otherwise specified, mastocytosis and MPN-unclassifiable (MPN-U) (2). As CML is invariably and specifically associated with Philadelphia chromosome (Ph), the others are operationally dubbed as Ph-negative MPNs (2).

Leukemic transformation (LT) of both Ph-positive and -negative MPNs is a well-known subject. The likelihood of second malignancies (SMs) as the result of the influence of the common molecular mechanisms, tyrosine kinase inhibitors (TKIs) or hydroxyurea (HU) has been reported as case reports. However sufficient data are not available in literature from Turkey about the frequency of SMs except LT in patients with MPNs. In this study, it was aimed to investigate the frequency of SMs in patients with Ph-positive or -negative MPNs.

MATERIALS and METHODS

This study was conducted as a retrospective, cross-sectional, single-center investigation. A total of 438 patients who were diagnosed with classical MPN according to WHO 2008 diagnostic criteria were included in the study. LT was defined as ≥ 20% blast ratio in bone marrow or peripheral blood. The patients who had been diagnosed with any SM before diagnosis of MPN and non-melanoma skin cancers were excluded. Diagnosis of SM was based on medical history, physical examination, imaging methods (magnetic resonance imaging or computed tomography scan) and pathological examinations.

Patient characteristics were examined using descriptive statistics. Continuous variables were given as mean ± standard deviation (SD), and categorical variables were defined as percentage. Chi-square and Student T-tests were used to compare proportions and means for categorical and continuous variables, respectively. Standardized incidence ratio for SMs were calculated as the ratio of the observed number of SMs in patients with MPNs to expected number of cancers in the general population of Turkey. Confidence intervals were calculated using the Passion distribution assumption. The variables which have significant p values ($p< 0.05$) and marginal insignificant p values ($p< 0.1$) in univariate analysis were included in multivariate analysis. All test significances were two-tailed. The SPSS statistical software (SPSS 17.0 for Windows, Inc., Chicago, IL, USA) was used for all statistical calculations.

RESULTS

The study included 223 males (50.9%) and 215 females (49.1%).While mean age of overall patients was 59.7 ± 15.7 years, mean age was 59.1 ± 16.3 and 60.2 ± 15.0 years for males and females, respectively. Mean duration from the diagnosis of MPN was 4.1 ± 3.7 years (3.9 ± 3.6 years for males and 4.3 ± 3.8 years for females). Distribution of the patients according to MPN diagnosis is shown in Table 1.

When SM frequency was analyzed among patients with MPNs, SM was detected in 15 (2 at the time of MPN diagnosis, 13 after MPN diagnosis) out of 438 patients (3.4%). There was SM in 10 (1 at the time of MPN diagnosis, 9 after MPN diagnosis) out of 223 male patients (4.5%); 5 (1 at the time of MPN diagnosis, 4 after MPN diagnosis) out of 215 female patients (2.3%). Distribution of SMs according to gender is given in Table 2 and 3.

LT was detected in 8 (6 AML, 2 ALL) out of 15 patients (1.9%). The average time to LT was found as 4.4 years (range 1-20 years).

When groups were compared with regard to gender, there was not a difference between groups with regard to age, duration of follow up, SM rates, LT rates ($p> 0.05$). A significant difference was detected only between MPN types ($p= 0.03$).

In this study, while cancer incidence rate was found as 1149.8/100.000 person-years for males with MPNs, it was 540.8/100.000 person-years for females. Relative risk (RR) was calculated as 4.67 (95% CI: 1.37;15.88) and 3.42 (95% CI: 0.55;21.18) for males and females,

Table 1. Distribution of patients according to diagnosis

	All patients (%)	Male patients (%)	Female patients (%)
CML	129 (29.5)	76 (34.1)	53 (24.7)
PV	118 (26.9)	62 (27.8)	56 (26.0)
ET	105 (24.0)	43 (19.3)	62 (28.8)
PMF	37 (8.4)	19 (8.5)	18 (8.4)
CNL	4 (0.9)	3 (1.3)	1 (0.5)
MPN-U	45 (10.3)	20 (9.0)	25 (11.6)
Total	438 (100)	223 (100)	215 (100)

CML: Chronic myelogenous leukemia, PV: Polycythemia vera, ET: Essential thrombocythemia, PMF: Primary myelofibrosis, CNL: Chronic neutrophilic leukemia, MPN-U: MPN-unclassifiable.

Table 2. Distribution of second malignancies in male patients

Type of second malignancy	Total (n= 223)	Philadelphia-positive MPNs (n= 76)	Philadelphia-negative MPNs (n= 147)
Acute myeloid leukemia	5 (2.2%)	2 (2.6%)	3 (2.0%)
Lung cancer	2 (0.9%)	2 (2.6%)	-
Liver neoplasm	1 (0.4%)	-	1 (0.7%)
Colorectal cancer	1 (0.4%)	1 (1.3%)	-
Prostate cancer	1 (0.4%)	-	1 (0.7%)
Total	10 (4.5%)	5 (6.6%)	5 (3.4%)

MPNs: Myeloprolifetarive neoplasms.

Table 3. Distribution of second malignancies in female patients

Type of second malignancy	Total (n= 215)	Philadelphia-positive MPNs (n= 53)	Philadelphia-negative MPNs (n= 162)
Acute myeloid leukemia	1 (0.5%)	-	1 (0.6%)
Acute lymphoid leukemia	2 (0.9%)	1 (1.9%)	1 (0.6%)
Colorectal cancer	1 (0.5%)	-	1 (0.6%)
Neuro-endocrine neoplasm	1 (0.5%)	-	1 (0.6%)
Total	5 (2.3%)	1 (1.9%)	4 (2.5%)

MPNs: Myeloprolifetarive neoplasms.

respectively according to International Agency for Research on Cancer (IARC) 2012 Turkey data (3).

DISCUSSION

LT of Ph-positive and -negative MPNs is a well-known subject. Although a couple of population-based studies are available in literature about SMs in Ph-positive MPNs, to the best of our knowledge this is the first study in Turkey investigating the frequency of SMs in this patient population.

Rebore et al.(4) analyzed a total of 2753 CML patients in their study conducted with Sweden National Cancer Registry and found that 145 (5.3%) of these patients developed a subsequent cancer. It was found that in the analysis of site-specific cancers, the researcher found increased risks for stomach cancer, skin cancer, cancer of the uro-genital tract and lymphoid leukemia, and no significant risks were noted for cancer of the buccal cavity, colorectal cancer, lung or bronchus cancer, melanoma, or non-Hodgkin lymphoma in comparison with the general population (4).

Voglova et al.(5) found that the age-standardized incidence rate of all malignant tumors except non-melanoma skin cancers was 6.76 (95% CI: 6.74; 6.78)/1.000 person-years in 2000-2007 while the incidence rate of SM in 708 CML patients from the Czech Republic treated with TKIs was 9.84 (95% CI: 6.20;13.48)/1.000 person-years, i.e. 1.5 fold higher, although the difference was statistically insignificant. Additionally the researcher detected that the distribution of SM types in CML patients treated with TKIs was similar to that in the age-standardized general Czech population (5).

Shah and Ghimire analyzed the SM rates among CML patients reported to Surveillance, Epidemiology, and End Results (SEER) database during pre- (1992-2000) and post- (2002-2009) era (6). The researcher found that among 8.511 adult CML patients, 446 patients developed 473 SMs (6). This study showed that risk of SMs is higher among CML patients and the rate of SMs for cancers of all sites in post-imatinib era were significantly higher compared to pre-imatinib era (6).

In addition to these population based studies, coexistence of MPNs with squamous cell cancer of the head and neck (7), gastrointestinal malignancy (8,9), breast cancer (10), plasmacytoma (11), chronic lymphocytic leukemia (CLL) (12) were also reported in several case reports.

In literature, data about SMs in Ph-negative MPNs are less than Ph-positive MPNs. Radaelli et al. (13) followed up 331 essential thrombocythemia (ET) patients during 108 months and detected SM development in 43 patients (15 hematological malignancies, 28 non-hematological malignancies). A significant correlation was found between SM development and alkylating agent use in this study (13).

Kissova et al.(14) analyzed a total of 172 Ph-negative MPN cases and found SM development in 15 patients,

they observed that 13 out of 15 patients were using HU. As a result, SM development was found significantly higher in HU using group with compared to the normal population in the same age group (14).

In patients with MPNs, coexisting CLL, Non-Hodgkin's Lymphoma, multiple myeloma cases are also available in literature (15-18).

In this study, cancer incidence rate was found higher (1149.8/100.000 person-years for males and 540.8/100.000 person-years for females with MPNs) compared with IARC data of Turkey (rate of non-cutaneous cancers standardized for age is 245.7/100.000 person-years for males, and 157.5/100.000 person-years for females).

Although this is the first study in Turkey investigating the SM development in patients with MPNs, it has some limitations. First is the small number of the study population. Further studies conducted with larger series are required to make in-group and inter-group comparisons with local and universal data. Second, we could not evaluate the risk factors including family history, genetic factors, drug use, and environmental factors.

In conclusion, SM frequency is clearly higher than normal population in patients with MPNs. We also found that both males and females have higher risk for SM development, consistently with literature. Whether the increased risk for SM development arises from treatment modalities or genomic instability is still of debate. However patients with MPNs should be carefully examined for SM symptoms and signs (6,13,14,16,19).

CONFLICT of INTEREST

The authors of this paper have no conflicts of interest, including specific financial interests, relationships, and/or affiliations relevant to the subject matter or materials included.

REFERENCES

1. Klco JM, Vij R, Kreisel FH, Hassan A, Frater JL. Molecular pathology of myeloproliferative neoplasms. Am J Clin Pathol 2010;133:602-15.
2. Tefferi A. Novel mutations and their functional and clinical relevance in myeloproliferative neoplasms: JAK2, MPL, TET2, ASXL1, CBL, IDH and IKZF1. Leukemia 2010;24:1128-38.
3. Available from: http://globocan.iarc.fr/Default.aspx
4. Rebora P, Czene K, Antolini L, Gambacorti Passerini C, Reilly M, Valsecchi MG. Are chronic myeloid leukemia patients more at risk for second malignancies? A population-based study.Am J Epidemiol 2010;172:1028-33.
5. Voglova J, Muzik J, Faber E, Zackova D, Klamova H, Steinerova K, et al. Incidence of second malignancies during treatment of chronic myeloid leukemia with tyrosine kinase inhibitors in the Czech Republic and Slovakia. Neoplasma 2011;58:256-62.
6. Shah BK, Ghimire KB. Second primary malignancies in chronic myeloid leukemia. Indian J Hematol Blood Transfus 2014;30:236-40.
7. Budrukkar A, Muttagi S, Shahid T, Chatturvedi P, Banavali S, Laskar SG, et al. Second primary head and neck squamous cell cancers with aggressive behavior in patients with chronic myeloid leukaemia. Br J Oral Maxillofac Surg 2012;50:504-7.
8. Slade R, Thomas WE. Gastrointestinal malignancies as a complication of chronic myeloid leukaemia. Br J Clin Pract 1990;44:76-8.
9. Frustaci A, Breccia M, Cannella L, Stefanizzi C, Alimena G. Occurrence of colon adenocarcinoma in chronic myeloid leukemia patients treated with imatinib: report of two cases and review of the literature. Leuk Res 2009;33:200-1.
10. Tillawi IS. Synchronous occurrence of Philadelphia chromosome-positive chronic myelogenous leukemia and breast cancer. Saudi Med J 2007;28:291-4.
11. Kim HJ, Kim MJ, Lee MJ, Ahn JH, Kim HS, Kim IS, et al. Coexistence of chronic myeloid leukemia and pulmonary plasmacytoma mimicking primary lung cancer. Int J Hematol 2010;92:651-4.
12. D'Arena G, Gemei M, Luciano L, D'Auria F, Deaglio S, Statuto T, et al. Chronic lymphocytic leukemia after chronic myeloid leukemia in the same patient: two different genomic eventsand a common treatment? J Clin Oncol 2012;30:e327-30.
13. Radaelli F, Onida F, Rossi FG, Zilioli VR, Colombi M, Usardi P, et al. Second malignancies in essential thrombocythemia (ET): a retrospective analysis of 331 patients with long-term follow-up from a single institution. Hematology 2008;13:195-202.
14. Kissova J, Ovesna P, Penka M, Bulikova A, Kiss I. Second malignancies in philadelphia-negative myeloproliferative neoplasms-single-center experience. Anticancer Res 2014;34:2489-96.
15. Zielinska P, Markiewicz M, Dzierzak-Mietla M, Koclega A, Helbig G, Kyrcz-Krzemien S. Coexistence of chronic lymphocytic leukemia and myeloproliferative neoplasm. Case Rep Oncol Med 2014;2014:512928. doi: 10.1155/2014/512928.
16. Trifa AP, Cucuianu A, Popp RA, Paţiu M, Selicean C, Militaru MS, et al. Concomitant myeloproliferative and lymphoid neoplasms in two patients positive for JAK2 V617F mutation. Case Report and Literature Review. Indian J Hematol Blood Transfus 2014;30:120-3.
17. Papageorgiou MV, Alexopoulou A, Kontopidou F, Filiotou A, Koskinas J, Pectasides D. Concomitant diagnosis of myeloproliferative neoplasm and non-Hodgkin's lymphoma in a patient with portal vein thrombosis. Anticancer Res 2011;31:1467-9.
18. Malhotra J, Kremyanskaya M, Schorr E, Hoffman R, Mascarenhas J. Coexistence of myeloproliferative neoplasm and plasma-cell dyscrasia. Clin Lymphoma Myeloma Leuk 2014;14:31-6.
19. Stein BL. Chronic myeloid leukemia and risk of second malignancy in two eras of treatment. Leuk Lymphoma 2012;53:1651-3.

How to cite:

Solmaz S, Korur A, Gereklioğlu Ç, Asma S, Büyükkurt N, Kasar M, et al. Second malignancies in Philadelphia-positive and-negative myeloproliferative neoplasms: A single center study. Gaziantep Med J 2016;22(2):72-75.