RESEARCH COMMUNICATION

Lymphoproliferative Disorders in Multiple Primary Cancers

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Abstract

Background: Cancer survivors are at increased risk of second cancers. Lymphoproliferative disorders (LPD) are common neoplasms that are primary or subsequent cancers in cases of multiple primary cancer. We here analyzed metachronous or synchronous LPD in multiple primary cancers. Methods: Between 2001 and 2010, LPD were assessed retrospectively in 242 multiple primary cancers patients. Results: Forty nine (20.2%) patients with LPD were detected. Six patients had two LPD where one patient had three LPD. The median age of patients was 60.5 years (range: 28-81). LPD were diagnosed in 29 patients as primary cancer, in 23 patients as second cancer, and in three patients as third cancer in multiple primary cancers. Primary tumor median age was 56 (range: 20-79). Diffuse large B cell lymphoma (n=16), breast cancer (n=9), and lung cancer (n=6) were detected as subsequent cancers. Alklylating agents were used in 19 patients (43.2%) and 20 patients (45.5%) had received radiotherapy for primary cancer treatment. The median follow-up was 70 months (range: 7-284). Second malignancies were detected after a median of 51 months (range: 7-278), and third malignancies with a median of 18 months (range: 6-72). Conclusions: In this study, although breast and lung cancer were the most frequent detected solid cancers in LPD survivors, diffuse large B cell lymphoma was the most frequent detected LPD in multiple primary cancers.

Keywords: Multiple primary cancers - lymphoproliferative disorders - diffuse large B cell lymphoma

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Introduction

Lymphoproliferative disorders (LPD) have three major categories; B-cell, NK/T-cell neoplasms, and Hodgkin lymphoma (HL) according to the World Health Organization (WHO) classification. Recently, the marked improvement was achieved in survival for patients with LPD however existence of second cancers risk has increased. LPD are the common neoplasms that have been primary or subsequent cancer in multipl primary cancers (MPC) (Dong et al., 2001; Swerdlow et al., 2008).

In actual cancer treatment, cure chance and controlling of advanced stage disease are increasing by early detection, as well as new agents with combined treatments. Cancer survivors comprise about 3.5% of the population and have increased risk for second cancers (8-16%) (Ries et al., 2006; Ng et al., 2008). MPC can reflect the influence of previous cancer therapy either chemotherapy or radiotherapy (RT), shared etiologic factors and genetic suspectibility (Cardous-Ubbink et al., 2007; Maedows et al., 2009). Leukemias and lymphomas arise in the first 5 years of treatment whereas solid cancers such as breast, lung, gastrointestinal, brain, genitourinary cancers arise after 5 years (Ganz, 2001; Dores et al., 2002; Hodgson et al., 2007). The treatment response of secondary cancers are not good. We analyzed LPD as primary and higher order cancer in MPC.

Methods and Results

Between 2001 and 2010, LPD's were assessed retrospectively in 242 MPC in the Medical Oncology Departments both of Hospital of Medicine Faculty, Gazi University and Numune Education and Research Hospital in Ankara. Basal cell carcinoma of the skin was excluded. The stage of the disease at diagnosis was not known. The cancer was accepted synchronous when the period between the primary and subsequent malignancy was less than 6 months.

LPD were detected in 49 patients whom 31 were male (64.6%), 18 were female (35.4%). Five patients had (10,2%) triple primary cancers and other five patients (10.2%) had synchronous cancers. The median age of patients was 60.5 years (range: 28-81). The median follow-up was 75.5 months (range: 7-284).

LPD were diagnosed in 28 patients as primary cancer and in 26 patients as subsequent cancers. Two LPD were diagnosed in six patients, three LPD in one patient. Primary tumor median age was 56 (range: 20-79) (Table 1) LPD subtypes in MPC are summarized in Table 2. Diffuse

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Table 1. Patient Characteristics

Median age	60,5 years	(R: 28-81)
Median follow-up	75,5 months	(R: 7-284)
Sex		
Man	31	63,7%
Woman	18	36.30%
Primary tumor age	60,5 years	(R: 20-79)
The interval of cancers		
Primary-second	55,5 months	(R: 7-284)
Second-third	22 months	(R: 7-72)
LPD's order		
Primary	27	
Second	24	
Third	2	
Subsequent solid malignancies		
Breast	9	
NSCLC	6	
Gastric	2	
Others	8	
RT exposure	20	45,5%
Alkylating agents	19	42,3%

* '*LPD:* Lymphoproliferative disorder, *NSCLC:* Nonsmall lung cancer, *RT:* Radiotherapy

Table 2. Lymphoprolifartive Disorders in Multiple Primary Cancers

LPD's in MPC's	Primary cancer	Subsequent Cancer
NHL	16	24
DLBCL	10	18
Maltoma	2	1
MZL	1	2
MF	1	-
T cell lymphoma	1	2
NK/T cell	-	1
Unknown subtype	1	-
HL	7	1
NSHL	2	1
LPHL	1	-
Unknown subtype	4	-
ALL	1	1
CLL	4	-

MPC; Multiple primary cancer, *NHL*; Nonhodgkins lymphoma, *DLBCL*; Diffuse large B cell lymphoma, *MZL*; Marginal zone lymphoma, *MF;* Mycosis fungoides, *HL*; Hodgkin lymphoma, *NSHL*; Nodular sclerozan HL, *LPHL;* Lymphocyte predominant HL, *ALL;* Acute lymphoblastic leukemia, *CLL;* Chronic lymphocytic leukemia

Table 3. Triple and Synchronous Malignancies

Triple malignancies	:	
DLBCL	AML	CNS lymphoma
Thyroid papillar Ca	Colon Ca	LPHL
ALL	Breast Ca (right)	Breast Ca (left)
LPHL	Breast Ca (right)	Breast Ca (left)
CNS lypmhoma	DLBCL	NK-T cell
Synchronous malignancies:		
Colon Ca	NSHL	
Thyroid papillar Ca	DLBCL	
NSCLC	LPHL	
HNSCC	AML	
NHL	GIST	

Ca; Cancer, *AML;* Acute myeloid leukemia, *CNS;* Cranial nervous system, *HNSCC;* head and neck squamous cell cancer *NHL;* Nonhodgkin lymphoma, *GIST;* Gastrointestinal stromal tumor.

large B cell lymphoma (DLBCL) was the most frequent LPD subtype in MPC as primary or subsequent whom three were cranial nervous system (CNS) lymphoma and two gastric DLBCL.

Subsequent LPD were mainly NHL. While DLBCL (n=16) was detected as subsequent LPD, breast cancer (n=9), non-small cell lung cancer (NSCLC) (n=6), gastric cancer (n=2), and others (n=8) were detected as subsequent solid cancers in MPC (Table 1). While alklylating agents were used in 19 patients (43.2%), 20 patients (45.5%) had received RT for primary cancer treatment. LPD were diagnosed in three patients after bone marrow transplantation for primary cancer treatment. Family history were determined for five patients. While the diagnosis of second malignancies was detected with median 55.5 months (range: 7-278), third malignancy was detected with median 22 months (range: 7-72). Nineteen (70.3%) of them were alive after the 77.5 months (range: 7-284) median follow-up.

Discussion

Second cancer is a disappointing outcome for long-term cancer survivors. Among cancer survivors, second cancer risk is higher than adjusted age groups (Dores et al., 2002; Hodgson et al., 2007). LPD have been primary or subsequent cancer in MPC (Dong et al., 2001; Tward et al., 2006; Demirci et al., 2010). We have observed 28 primary LPD and 24 subsequent LPD in present study. In our study population, subsequent cancers were diagnosed earlier than previous reports in the literature. Second cancer was diagnosed after 55.5 months of primary cancer, third cancer was diagnosed after 22 months of second cancer. In a study, 79 second malignancies were observed with median five years or more after the diagnosis in 1368 cancer survivors. The second malignancies occurred on average 17.1 years after diagnosis of the primary cancer. In previous studies, despite solid tumor risk was much higher than that of hematolymphoid malignancies (Cardous-Ubbink et al., 2007), in present study both of LPD and solid tumor incidence were equal.

In current study, two triple cancer patients whom primary cancers were HL and ALL had bilateral breast cancer as subsequent cancers. The reason was the early age of diagnosis and treatment with alklyating agents and RT. Besides, nearly half of patients received RT and alklyating agents in our study. Chemotherapy agents can cause cancer by different mechanisms. Patients with HL and NHL are treated with combination chemotherapy regimens containing alkylating agents, topoisomerase inhibitors and anthracyclines. Risk is enhanced with cumulative doses and added RT. We used rituximab and anthracycline based (CHOP like, ABVD) regimens mostly. Solid cancers account for the majority of excess cancers. However solid cancers are seen later than leukemia and lymphoma and frequently associated with RT. Especially, enhanced doses and early diagnosis of age are important risk factors (Neglia et al., 1991; Hodgson et al., 2007). Patients with HL who are diagnosed under age 16, received high dose alkylating agents and bone marrow transplantation have increased risk for developing a second malignancy (Travis

et al., 1995; Armitage et al., 2000; Bassal et al., 2006). The risk increases with years of survivorship. At 5 years the risk is 2%, which increases to 20% after 20 years (Maedows et al., 2009). Hodgson et al observed 1490 MPC in HL survivors. In 12.2 median follow-up, second cancers risks were depend on age at HL diagnosis and attained age (Hodgson et al., 2007). Although HL at age 20 had 50-year cumulative incidence of 66% in women, second cancer incidence was lower in men (Dores et al., 2002). In our study, the incidence of subsequent cancer in man was higher than female.

In recent studies, cumulative risk at over 20-years follow-up was 2.6 to 4.9% in long term survivors (Olsen et al., 1993; de Vathaire et al., 1999; Jenkinson et al., 2004). In a study, female gender, younger age at diagnosis, primary HL and soft tissue sarcoma, and increased exposure anthracyclines/ epipodophilotoxins were risk factors in 13.581 patients with 5-year survivors (Neglia et al., 2001). In Chaturvedi et al's study, enhanced risk was detected for NHL and AML in the RT group however no statistically significant increase was observed in either treatment group for HL in cervical cancer survivors (Chatuverdi et al., 2007). Although the second cancer outcomes are not good, most of our patients are still alive after median 5 years of first cancer. In a study, 5490 second cancers were observed and overall elevated risk was detected as 14% in NHL survivors. Although gender and race did not affect the risk, age especially 30-49 years has elevated the risk (Dores et al., 2006).

There have reported significant excesses of lung cancer, melanoma, soft tissue sarcoma, NHL, AML, genitourinary cancers, head and neck cancer in lymphoma survivors (Travis et al; 1993;1995; Armitage et al., 2000; Dong et al., 2001; Brennan et al., 2005; Bassal et al., 2006, Dores et al., 2006). Hisada et al. (2007) showed among 10,000 hairy cell leukemia patients, were at increased risk of thyroid cancer, HL, and NHL. We confirm this finding, in our study, DLBCL as a subsequent cancer was the most frequent subtypes of NHL. Although current modern chemotherapy regimens and RT technics are reduced the incidence second HL, NHL especially DLBCL have increased. The shortage of present study is undetailed treatment information that would have describe second cancer risk estimates.

In this study, although breast and lung cancer were the most frequent detected cancers in LPD survivors, DLBCL was the most frequent detected primary and subsequent cancer in MPC. In conclusion, LPD are frequent cancers in MPC and detection and early diagnosed programmes should be performed to cancer survivors lifelongly. By this way, subsequent cancers can be detected earlier, and long term survival can be improved.

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