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The clinicopathologic features of multiple primary malignancies in hematology: A cross sectional descriptive study

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Abstract

In Turkish literature there are very few studies regarding multiple primary malignancies (MPM). The aim of this study was to analyze the synchronous and the metachronous malignancies that occurred with a hematologic malignancy. All the patients with a hematologic malignancy were enrolled in this cross-sectional, definitive retrospective study. Data were obtained from the medial records. Patients' characteristics including demographic features, treatment protocols and overall survival (OS) were recorded. Among 663 patients with a hematologic malignancy, there were 26 patients with MPMs (3.9%). Synchronous malignancies constitute 0.9% and metachronous malignancies were present in 3%. In men diffuse large B-cell lymphoma (DLBCL) and non-small cell lung carcinoma (NSCLC) and in women breast and acute myeloid leukemia were the most common primary and secondary MPMs respectively. The mean cumulative OS of all patients with MPMs was 246.3±33.4 months and the 5 years-OS was 91.3%. In synchronous MPMs the most frequent concomitant tumors were DLBCL and NSCLC. In metachronous tumors the median time interval between first and second malignancies was 69.5 months (range: 31-312). In four patients there were three MPMs. After radiotherapy three patients developed breast, thyroid and skin cancers and in one patient who received radioiodine for the treatment of thyroid carcinoma, DLBCL had developed. The chemotherapeutic agents applied for the primary malignancies consisted of alkylating agents, antimetabolites, anthracyclines, topoisomerase II inhibitors, monoclonal antibodies and mitotic inhibitors. In 75% of the patients with DLBCL who had received R-CHOP chemotherapy regimen, NSCLC had developed during the follow-up period. In conclusion secondary malignancies with hematologic malignancies are not rare and the clinicians should keep the possibility of secondary malignancies in mind and be suspicious during diagnostic evaluations. Warning with regard to the risk of development of secondary malignancies due to the primary treatment should be given to any patient with a hematologic malignancy.

Keywords: Multiple primary malignancy, hematologic malignancy, synchronous malignancy, metachronous malignancy

Introduction

Multiple primary malignancies (MPMs) are the malignancies with different histological origins that occur at different sites in the same person [1]. Their exact incidence is not known; however, it is believed that the incidence tends to increase. This increase may be attributed to the recent therapeutic and diagnostic improvements. In the USA, cancer survivors constitute 5% of the population and the number of survivors is projected to increase by 29.1% by the year 2029 [2]. The trend is similar in our country; by the year 2030, the incidence of new cancer cases is estimated to increase by 75% [3]. All these cancer survivors have a higher risk of developing second cancer than adjusted age groups (8-16%) [4-6].

In a large study, the risk of developing a secondary cancer was found to be increased six times compared to the basal population risk [7]. As the number of long-term survivors increases, the risk of developing a secondary malignancy increase. This may be due to the presence of genetic cancer-predisposing syndromes, immunologic defects, prolonged exposure to genotoxic treatment modalities including chemotherapy and radiotherapy [8].

The Surveillance Epidemiology and End Results (SEER) Program which is the main source for cancer statistics in the United States and provides epidemiologic information on the incidence and survival rates of cancer to reduce the cancer burden, classified multiple malignancies as being synchronous if diagnosed within two months of each other and metachronous if diagnosed more than two months apart [9]. In hematologic malignancies, the development of asynchronous or metachronous secondary malignancy is not uncommon. New hematologic malignancies may arise in the first five years and solid cancers tend to develop

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after the first five years following the initial treatment in these patients [4,5,10]. Over 20 years of follow-up, the cumulative risk of secondary cancer has been reported to be 2.6 to 4.9% [11,12]. In a study, the overall elevated risk was detected as 14% in non-Hodgkin lymphoma survivors [13]. Breast and lung cancers are the most frequently detected solid organ malignancies in lymphoproliferative disorders [14].

In Turkish literature, there are very few studies regarding MPMs. [14-16]. Studies on synchronous or metachronous malignancies with hematologic malignancies are much more limited. This study aimed to analyze the synchronous and the metachronous malignancies that occurred with hematologic malignancy.

Materials and Methods

All the patients who were diagnosed to have or followed-up with hematologic malignancy in Adana Baskent University Medical Faculty Department of Hematology between January 2007 and July 2019 were enrolled in this cross-sectional, definitive retrospective study. Data were obtained from the medical records, either from patient files or the hospital's electronic database. Informed consent was obtained from alive patients. Institution's ethics committee's approval was obtained (KA19/283).

The criteria of Warren and Gates for diagnosis of MPMs were used [1]. Briefly, tumors with definitive features of malignancy, separate and distinct from the index tumor, and the tumors that have no possibility of being metastasis of the index tumor were

included. Only the patients with histopathologic confirmation were included. Tumors were grouped as synchronous if they were diagnosed within two months of each other and metachronous if diagnosed more than two months apart.

Patients' characteristics including demographic features, tumor sites, stages of the hematologic tumors, pathologic results, duration between the appearance of primary and secondary or tertiary tumors, treatment protocols, and overall survival (OS) after the diagnosis were recorded.

Statistical analysis was accomplished by using SPSS version 22 (IL, USA). Nominal data are expressed as percentages. Continuous data were expressed as means $\pm$ standard deviation if normally distributed and as median (minimum-maximum) if not normally distributed. Survival analysis was performed with Kaplan - Maier test and mean survival time is shown as mean $\pm$ standard error. Chi-square, t-test, and Mann-Whitney U tests were used where appropriate. A p-value of ≤ 0.05 was considered significant.

Results

Among 663 patients with hematologic malignancies assessed between the study period, there were 26 patients with MPMs with an incidence of 3.9%. The clinicopathological features are depicted in Tables 1-3. The mean age of the patients with MPMs was 57.0 ± 11.6 years (range 25 – 81 years). There were 17 males (65.4%) and nine females (34.6%) with a male to female ratio of 1.9.

Table 1. Clinicopathologic features of patients with two synchronous multiple primary malignancies

Age	Sex	First primary site	Treatment	Second primary site	Treatment	Smoke	FHC	Death	OS
57	M	Lung, non small cell carcinoma	Carboplatin, Paclitaxel Cisplatin, Gemcitabine	Diffuse large B cell lymphoma	RT	+	-	-	24
65	M	Diffuse large B cell lymphoma	-	Lung, non small cell carcinoma	RT	+	-	-	56
66	M	Lung, non small cell carcinoma	Carboplatin, Paclitaxel Cisplatin, Gemcitabine	Diffuse large B cell lymphoma	-	+	-	-	43
62	F	Breast invasive ductal carcinoma	Anastrozele	Multiple myeloma	Bortezomib, Lenalidomide, H-Melphalan AutoSCT	+	-	-	46
59	M	Lymphoplasmocytic lymphoma	Cyclophosphamide, Vincristine, Rituximab	Plasma cell dyscrasia	Bortezomib, Dexamethasone	-	-	-	96
53	F	Thyroid papillary carcinoma	Radioactive iodine	Breast invasive ductal carcinoma	Surgery, Anastrozole	-	-	-	18

FHC: Family history of cancer, OS: Overall survival, M:Male, F:Female, RT: Radiotherapy, H: High, AutoSCT: Autologous stem cell transplantation

The mean age at diagnosis of the primary tumor was significantly younger in women when compared to men (49.4 ± 13.5 vs. 61.1 ± 8.4 years, $p=0.038$). Synchronous malignancies were detected in 23.1% of the patients (n:6) and 76.9% had metachronous MPMs (n:20) (Tables 1 and 2). In 4 of the metachronous patients, there were three primary cancers (Table 3). The mean cumulative OS of all patients with MPMs was 246.3 ± 33.4 months and the five years-OS was 91.3%.

The total number of malignancies in 26 patients was 56, and overall the most frequent malignancy was non-small cell lung carcinoma with an incidence of 23.2% (n:13), followed by diffuse large B cell lymphoma (DLBCL) which was seen in 16.1% (n:9) of the patients. The most frequent primary malignancies were DLBCL (30.8%, n:8/26) and invasive ductal breast carcinoma (19.2%, n: 5/26). When analyzed concerning gender, DLBCL was the most common primary cancer found in 47.1% of all the males and breast

Table 2. Clinicopathologic features of patients with two metachronous multiple primary malignancies

Age	Sex	First site	Treatment	Second site	Treatment	Stage	Time interval	Smoke	FHC	Death	OS
44	M	DLBCL	R-CHOP	Lung, non small cell carcinoma	Cisplatin, Pemetrexed, Carboplatin, Paclitaxel, RT	R-IPI	23	-	+	+	31
63	F	Breast, invasiv ductal	Epirubicin, Cyclophosphamide	Follicular lymphoma	-	FLIPI-H	96	-	+	-	144
66	M	Myelodysplastic Synd	Decitabine	Lung, small cell carcinoma	Surgery	IPSSR-H	7	+	+	-	39
33	F	Breast invasive ductal	Carboplatin, Paclitaxel, Tmx, Anastrozole	Acute myeloid leukemia (transformed from MDS)	Induction/consolidation	High	34	-	-	-	44
50	M	Multiple myeloma	VAD, H-Melphalan, AutoSCT	Lung, non small cell carcinoma	-	ISS-1	36	+	-	+	40
68	M	Multiple myeloma	VAD, H-Melphalan, Lenalidomide	Lung, non small cell carcinoma	Carboplatin, Paclitaxel	ISS-1	24	+	-	-	48
58	F	Breast invasive ductal	Epirubicin, Cyclophosphamide, Dosetaxel, Anastrozole RT	Acute myeloid leukemia	Induction/consolidation	Low-Int	21	-	-	-	77
81	M	Multiple myeloma	Bortezomib, Melphalan, Lenalidomide	Prostate adenocarcinoma	RT	ISS-2	17	-	+	-	72
58	M	DLBCL	R-CHOP	Lung, non small cell carcinoma	Carboplatin, Paclitaxel	R-IPI-2	12	+	-	+	72
63	M	Multiple myeloma	VAD H-Melphalan, Bortezomib, AutoSCT	Kidney renal cell carcinoma	Surgery	ISS-2	48	+	-	-	96
67	M	Hairy cell leukemia	Cladribine, Rituximab	Colon adenocinoma	Neo-adjuvant CT, Surgery	-	48	+	-	-	60
40	F	Ovarian adenocarcinoma	Surgery, Carboplatin, Paclitaxel, Cisplatin, Cyclophosphamide	Acute myeloid leukemia (transformed from MDS)	Induction/consolidation	High	312	-	+	+	312
57	M	Hairy cell leukemia	Cladribine, Rituximab	Lung, non small cell carcinoma	Carboplatin, Doseaxel	-	98	+	+	-	108
57	F	Breast invasive ductal	Surgery	DLBCL	Rituxumab, V, Etoposid	R-IPI-3	72	-	-	+	77
50	M	Acute myeloid leukemia	Idarubicin, Cytarabine, Tretinoi, AlloSCT	Lung, non small cell carcinoma	Carboplatin, Paclitaxel, RT	Int.	48	+	-	-	67
54	F	Thyroid papillary, Carcinoma	Radioactive iodine	DLBCL	R-CHOP	R-IPI-3	25	-	+	-	33

FHC: Family history of cancer, OS: Overall survival, M:Male, F:Female, DLBCL: Diffuse large B cell lymphoma, RT: Radiotherapy, R-CHOP: Rituximab - cyclophosphamide, doxorubicin, vincristine, prednisolone, VAD: Vincristine, doxorubicin, dexamethasone, AutoSCT: Autologous stem cell transplantation, MDS: Myelodysplastic syndrome, H: High, ISS: International Staging System, R-IPI: Revised International Prognostic Index, Int: Intermediate, IPSS-R: Revised International Prognostic Scoring System, FLIPI: Follicular Lymphoma International Prognostic Index.

carcinoma was the most common malignancy with an incidence of 55.6% among females with MPM. Non-small cell lung carcinoma was the most frequent secondary malignancy constituting 46.2% (n:12/26) of all secondary malignancies followed by acute myeloid leukemia (AML) (11.5%, n: 3/26). In 64.7% of males, the secondary malignancy was non-small cell carcinoma and in 33.35 of females, it was acute myeloid leukemia.

There were six synchronous MPMs (Table 1). The most common concomitant tumors were non-small cell lung cancer and DLBCL (50% of synchronous malignancies). All three patients with lung carcinoma had a cigarette smoking history. Relevant therapies including chemotherapy and radiotherapy had been given for the treatment of each malignancy (Table 1). There were no deaths during the study period and the median OS was 44.5 (18-96) months in these patients.

There were 16 patients with metachronous two primary malignancies (Table 2). The most frequent primary malignancies were invasive ductal breast carcinoma and multiple myeloma; both were present in 25% of the patients. The most frequently diagnosed secondary metachronous malignancy was non-small cell lung carcinoma, which developed in 50% of these 16 patients. The median time interval between the first and second malignancies was 69.5 months (range: 31-312). The chemotherapeutic agents applied for the primary malignancies consisted of alkylating agents, antimetabolites, anthracyclines, topoisomerase II inhibitors, monoclonal antibodies and mitotic inhibitors (Table 2). Most of the hematologic malignancies were in an advanced stage. During the study period, 31.5% of the patients died. The estimated cumulative overall survival was 219.2 ± 43.3 months with a five years-OS of 86.6%.

Table 3. Clinicopathologic features of patients with three multiple primary malignancies

Age	Sex	First site	Trt	Second site	Trt	Time interval	Third site	Time interval	Trt	Death	OS
62	M	DLBCL	R-CHOP	Lung, non small cell carcinoma	RT	36	Skin, basal cell carcinoma	48	Excision	-	96
61	M	DLBCL	R-CHOP	Prostate adenocarcinoma	RT	12	Thyroid Papillary carcinoma	12	Radioactive iodine	-	60
25	F	Brain, Glioblastoma	Temozoamide, RT	Breast invasive ductal	Surgery, paclitaxel	72	Precursor B cell 21 leukemia	21	Induction	-	96
64	M	DLBCL	R-CHOP, H-melphalan, AutoSCT	Skin basal cell carcinoma	Excision	28	Lung non small cell carcinoma	22	Carboplatin Paclitaxel	-	51

Trt: Treatment, FHC: Family history of cancer, OS: Overall survival, M:Male, F:Female, DLBCL: Diffuse large B cell lymphoma, RT: Radiotherapy, R-CHOP: Rituximab - cyclophosphamide, doxorubicin, vincristine, prednisolone, AutoSCT: Autologous stem cell transplantation, H: High

In four patients, third malignancy developed after a median of 21.5 months (range: 12-48) from the second malignancy. In 3 of these patients, the primary malignancy was DLBCL and they had been treated with R-CHOP chemotherapy (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisolone) and in two of them, one of the other malignancies was non-small cell carcinoma. None of these patients die and the median overall survival was 78 months (range: 51-96).

Half of the patients (50%) were smokers, males having a significantly higher proportion (70.6% vs. 11.2%, $p=0.002$). A family history of malignancy was confirmed in 34.6% of the patients and there was no difference between males and females.

Discussion

Lack of knowledge in variables about a condition in a population may make it impossible to conduct investigations about causality. In such cases, cross-sectional descriptive studies are mandatory and only such studies help to fill the information gap [17]. This cross-sectional study is aimed to provide descriptive data on synchronous and metachronous multiple primary malignancies accompanying at least one hematologic malignancy and is one of the very few, if not the only, studies on this subject in our country.

In a large study from Turkey, the incidence of MPMs was 1.4% [15]. The hematologic malignancies were reported to constitute 12.3% of all single and 11.9% of all multiple primary malignancies and among the MPMs, B cell neoplasms were the most frequent ones [15]. However, the incidence and features of multiple primary tumors in hematologic malignancies were not known in the Turkish population. The incidence of MPMs in hematologic malignancies was found to be 3.9% in our studied population. Synchronous malignancies constitute 0.9% of all hematologic malignancies, and metachronous malignancies were present in 3% of the whole population. The most frequent primary and secondary malignancies were DLBCL and non-small cell lung carcinoma respectively. In men, this order is the same; however, in women, breast carcinoma was the most common primary and AML was the most common secondary MPMs. In men and the whole population, DLBCL and non-small cell lung carcinomas were the most frequent concomitant tumors. In women, breast carcinoma and AML were the most frequent concomitant tumors.

The role of radiotherapy and anti-cancer chemotherapeutics on the development of a secondary carcinoma in pediatric or adult cancer survivors is well known. [18]. It has been reported that after radiotherapy breast, lung, and thyroid carcinomas, osteosarcoma and acute lymphoblastic leukemia may develop [19]. Radioactive

iodine has been related to the development of secondary cancers such as leukemia, hematological malignancies, salivary gland cancer, colorectal cancer and soft tissue sarcoma [20]. In the present study, after radiotherapy 3 patients developed breast, thyroid and skin cancers and in one patient who received radioiodine for the treatment of thyroid carcinoma, DLBCL had developed after about two years. Alkylating agents, platin based chemotherapeutics, anthracyclines and topoisomerase-II inhibitors have been related to secondary malignancy development, especially AML [21,22]. These agents pose the highest risk of initiating carcinogenesis especially in normal cells sensitive to chemotherapy like cells of the bone marrow, hair follicles, and the epithelial cells of the gastrointestinal tract. Therefore, there is an increased risk of development of secondary hematologic cancers such as leukemia and lymphoma [23]. AML had developed in 15% of the patients in the metachronous group as a secondary malignancy, following the treatments for breast and ovarian carcinomas. Alkylating agents and radiotherapy were given for the treatment of the primary malignancies. Again, after treatment of breast cancer with an alkylating agent and an anthracycline, follicular lymphoma had developed in another female patient. It was observed that in 75% of the patients with DLBCL who had received R-CHOP chemotherapy regimen in the metachronous group, non-small cell lung carcinoma had developed during the follow-up period. Alkylating agents and anthracyclines that are components of the R-CHOP regimen given for lymphoma treatment have been related to secondary cancers including solid tumors [24]. Several studies have observed that alkylating chemotherapy significantly increases the risk of particularly lung cancer [25,26]. For lung cancer, the increased relative risk from smoking appeared to multiply the elevated risks from chemotherapy and radiotherapy [25]. From this point, it would be a good clinical practice to give counseling to the patients about the secondary cancer development potential of such chemotherapeutic agents especially in the smoking setting.

The male to female ratio of MPMs in hematologic malignancies was 1.9, and MPMs seemed to develop in younger ages among women cancer survivors. These findings in the present study are consistent with the findings of the studies about the MPMs conducted in the Turkish population [16,27]. Lung has been reported to be the most common secondary tumor followed by breast as in our study [16]. Although those studies reported results all of the MPMs and no studies are assessing only the MPMs with a hematologic malignancy like this study, the results are in accordance.

The main limitation of this study was that it was impossible to analyze the exact causality between clinicopathologic features, including treatment regimens and risk of developing a secondary malignancy due to the retrospective design of the study and there would be too many confounding factors. Previous cancer treatments, genetics, immunity, hormonal status, environmental factors and lifestyle play a complex role in the development of secondary malignancy and it is difficult to conduct a causality analysis. However, this study aimed to present baseline data about a critical clinical situation as the secondary malignancies begin to constitute the second most frequent cause of deaths from cancers following the relapse [22]

Conclusion

In conclusion, knowledge about the clinical features of the MPMs that accompany a hematologic malignancy is crucial as the number

of cancer survivors increases with improvements in diagnostic and therapeutic strategies as well as management of complications. This study provides an awareness of the secondary malignancies in hematology. Clinicians should keep the possibility of secondary malignancies in mind and be suspicious during diagnostic evaluations. Warning about the risk of development of secondary malignancies due to the primary treatment should be given to any patient with hematologic malignancy.

Competing interests

The authors declare that they have no competing interest.

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Ethical approval

Institution's ethics committee's approval was obtained with the number KA19/283.

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