Evaluation of the Patients with Hematological Malignancies along with Synchronous or Metachronous Solid Tumors

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ABSTRACT

Although novel therapeutic strategies, expected lifetime of patients with multiple primary tumors is still short. However early diagnose of solid tumors can improve survival. Espe-cially PET CT evaluation can be an important guide to detect second primary tumor. In hematological malignancies particularly in lymphomas and myeloma, in those solid tumors can be misdiagnosed as progression. So discrimination is more difficult in these cases. Therefore we planned to focus on diagnostic procedures, histological types, tumor sites and survival parameters as objec-tives of this study. Patients with two cancers with hematological malignancies and solid tumors or second hematological malignancy were enrolled. An exclusion criterion was treatment-associated hematological malignancies. For statistical analysis, the SPSS program was used. Writ-ten informed consent was taken from all patients. This study was reviewed and approved by local ethics committee. Fourty five patients were enrolled to study. Among these 45 cases of multiple primary malignancies, 20 of them were synchronous (44.4%) and 25 of them were metachronous (55.6 %) (p= 0.63). The most frequently diagnosed hematological malignancy in this double primary cancer study was Non-Hodgkin's lymphoma (23 cases; 51.1%). During follow up, 22 of 45 patients died. Median interval between the diagnosis of two tumors was 11 months (95% CI: 1-168). 36 months survival was 65.5% (95% CI: 48. 0-78.4 months). New cancers can develop at the same time or after treatment of one cancer. The incidence of second primary cancers on patients with hematological malignancies is ex-pected to increase due to the better screening programs for early detection of malignancies as well as considerable improvement in their treatment, using novel imaging techniques and longer life expectancy.

Keywords: Double primary tumor, Synchronous tumor, Metachronous tumor, PET CT

INTRODUCTION

Despite the improvements in cancer therapy, malignancies are still one of the important causes of death worldwide. Therapeutic strategies in cancer therapy have increased with novel approaches such as monoclonal antibodies, immunotherapy modalities and specific molecular inhibitors. These approaches improved survival in both hematological malignancies and solid tumors. With the development of new therapeutic options, cancer patients became to have longer survival. However, patients with multiple cancers have still poor prognosis.[1]

On the other hand, prolonged life span of cancer patients, it is estimated that there will be more patients who develop multiple cancers in the future. These multiple cancers can be classified as "synchronous" or "metachronous". Synchronous cancers were defined as those occurring within 6 months of the first primary cancer, while metachronous cancers were defined as those occurring more than 6 months later.[2]

Although it is difficult to diagnose synchronous or metachronous tumors, we assume that advanced diagnostic tools such as positron emission tomography (PET/CT) can guide to suspect multiple primary tumors in hematological malignancies.

Another entity in metachronous tumors is treatment-associated secondary malignancies. Those are developed due to chemotherapy and/or radiotherapy which are used for primary cancer before. Many drugs and the mechanisms about treatment-associated malignancies have been studied so far.[3] In this retrospective study, we aimed to evaluate the patients with hematological malignancies along with synchronous or metachronous solid tumors in our center to determine the impact of diagnostic procedures on clinical outcomes in this patient group. In addition, comparison of survival data of these double primary cancer patients with current scientific data is also aimed. Therefore we planned to focus on diagnostic procedures, histological types, tumor sites and survival parameters as objectives of this study.

PATIENTS and METHODS

Patients

Patients with two cancers with hematological malignancies and solid tumors or second hematological malignancy whom were diagnosed between January 2012 and December 2018 in Medstar Antalya Hospital were included to this retrospective study. Inclusion criteria were; age ≥18 years and histopathological or immunohistochemically proven of both tumors. Also, two hematological malignancies which are not accepted as treatment-associated were included as well. An exclusion criterion was treatment-associated hematological malignancies. Various parameters like patient's age at time of each cancer diagnosis, sex, being synchronous or metachronous, site of origin, diagnostic methods and clinical stage have been recorded.

For statistical analysis, the SPSS (version 20.0; SPSS Inc., Chicago, IL) program was used. Differences between groups were evaluated by the chi-square or fisher exact test. Survival probabilities were estimated using the Kaplan-Meier method. All P values < 0.05 were considered statistically significant.

Written informed consent was taken from all patients. This study was reviewed and approved by local ethics committee of Memorial Hospitals Group.

PET-CT Scan

The imaging was performed with Siemens Biograph mCT 20. Images were obtained from vertex to mid-thigh in standard supine position when blood glucose levels of all the patients were below 200 mg/dl following minimum 6 hours of fasting. CT component of the PET/CT scan was performed in the standard diagnostic dose automatically determined with dose reduction programs and by intravenous administration of 100 ml 300 mg/ml non-ionic contrast agent to the patients, unless contraindicated. 3,7 MBq/kg of 18F-Fluoride FDG was intravenously administered to the patients. The PET/CT scan was performed 60 minutes after FDG injection. The images obtained were evaluated by two physicians, including one radiologist and nuclear medicine specialist, and one nuclear medicine specialist, and were reported by consensus.

Technical Parameters of the PET-CT Scan

The CT component of PET/CT scan was performed by monophasic injection at 1 ml/s and a 60-sec delayed acquisition with 1.5 mm slice thickness and 3 mm interslice intervals, using a 60-200 mA/s, 100-120 kV automatic dosing software (CareDose™) and an automatic injector system (Medrad). The PET scan was performed with 3-D acquisitions and a scan time of 2 min per bed position, applying scatter correction with an iterative algorithm (4 iterations, 8 subsets, and a FWHM filter of 4 mm).

Evaluation Criteria of Patients via PET-CT

The lesions that were not consistent with metastatic spread of primary tumor, normal physiological biodistribution pattern, infection or granulation, and that had a radiologic morphology which was not consistent with metastasis but with the cancer of the tissue where they are localized were reported as indicative of second primary cancer; biopsy sampling was recommended for the lesions. Com-

Table 1. Patient characteristics

	n= 45
Age at diagnosis, median (range), years	62 (26-89)
Male, n (%)	24 (53.3)
Primary hematological malignancies, n (%)	
Non-Hodgkin's lymphoma	23 (51.1)
Hodgkin's lymphoma	1 (2.2)
MM	7 (15.6)
AML	1 (2.2)
CML	2 (4.4)
CLL	8 (17.8)
MPN	2 (4.4)
Plasmacytoma	1 (2.2)
Stage of hematological malignancies, n (%)	
Advanced	25 (64.1)
Second primary malignancies, n (%)	
Lung	16 (35.6)
Soft tissue sarcoma	1 (2.2)
Kaposi sarcoma	1 (2.2)
Esophagus epidermoid cancer	1 (2.2)
Breast	7 (15.6)
Cervix	3 (6.7)
CML	1 (2.2)
Cholangiocarcinoma	2 (4.4)
Pancreas adenocarcinoma	1 (2.2)
Skin	3 (6.7)
Papillary thyroid carcinoma	1 (2.2)
GIST	1 (2.2)
Gastric adenocarcinoma	1 (2.2)
Ovarium adenocarcinoma	1 (2.2)
Colon adenocarcinoma	2 (4.4)
Liver adenocarcinoma	1 (2.2)
Larynx adenocarcinoma	1 (2.2)
Endometrium adenocarcinoma	1 (2.2)
Stage of second malignancy, n (%)	
Advanced	20 (44.4)

MM= multiple myeloma; AML= acute myeloid leukemia; CML= chronic myeloid leukemia; CLL= chronic lymphocytic leukemia; MPN= myeloproliferative neoplasm; GIST= gastrointestinal stromal tumor

puted tomography images and metabolic activity were interpreted together during the evaluation; the lesions were also evaluated with their radiological features apart from their hypometabolic patterns. Only the newly developed and histopathologically proven cases were included in the study.

RESULTS

As a total of 45 patients were enrolled to study. Among these 45 cases of multiple primary malignancies, 20 of them were synchronous (44.4%) and 25 of them were metachronous (55.6%). However there was no significant difference between the numbers of two groups p= 0.063). Out of 45 patients, 21 (46.7%) were females and 24 (53.3%) were males. Among our patients there was no statistical difference between the numbers of gender (p= 0.81). The median age at the diagnosis of primary hematological malignancy was 62 years (26-89). Basic characteristics of the patients are summarized in Table 1.

The most frequently diagnosed hematological malignancy in this double primary cancer study was Non-Hodgkin's lymphoma (NHL) (23 cases; 51.1%) followed by chronic lymphocytic leukemia (CLL) (8 cases; 17.8%) and multiple myeloma (MM) (7 cases; 15.6%) followed by other hematological malignancies. Histological subtypes of 23 NHL patients were; 6 (26.1%) diffuse large B cell lymphoma, 3 (13.0%) peripheral T cell lymphoma, 5 (21.8%) low grade lymphomas (marginal zone and not other specified), 6 (26.1%) follicular lymphoma, 1 (4.3%) Richter transformation of low-grade lymphoma, 1 (4.3%) Burkitt's lymphoma and 1 (4.3%) hairy cell leukemia.

The most common site of 45 second primary malignancy was lung (16 cases; 35.6%) followed by breast (7 cases; 15.6%), cervix and skin cancers (3 cases; 6.7% each) and then other tumors. Less than half of the patients have advanced tumor (44.4%). Except one patient, all patients have solid tumors diagnosed during the course of hematological malignancies. None of the patients had been diagnosed with solid tumor before the diagnosis of hematological cancer. Cancer types of synchronous group are summarized in Table 2.

In the group of patients with metachronous tumors, lung cancer was the most commonly diagnosed type of solid tumors as well as the synchronous tumors group. All of the types of cancers in this group are summarized in Table 3. Another interesting finding in this group was coexistence of two hematological malignancies like chronic myeloid leukemia (CML) and NHL; those are derived from two different hematopoietic cell lines.

Table 2. Distribution of synchronous tumors by site (n= 20)

	NHL n (%)	MM n (%)	CLL n (%)	Plasmacytoma n (%)	Total
Lung	7 (35)	1 (5)	1 (5)	1 (5)	10 (50)
Sarcoma	1 (5)				1 (5)
Esophagus	1 (5)				1 (5)
Breast	1 (5)	1 (5)			2 (10)
Colangiocarcinoma		1 (5)			1 (5)
Ovarium	1 (5)				1 (5)
Colon	1 (5)				1 (5)
Cervix	1 (5)		1 (5)		2 (10)
Endometrium	1 (5)				1 (5)
Total	14 (70)	3 (15)	2 (10)	1 (5)	20 (100)

NHL= Non-Hodgkin's lymphoma

During follow up, 22 (48.9%) of 45 patients died. Figure 1 shows the Kaplan Meier's survival analysis of patients.

Median follow up was 31 (%95 CI: 2-204) months and the median time between the diagnosis of first cancer and death was 108 (%95 CI: 20-204) months. Twelve of 22 deaths (54.5%) were within the first 24 months of first cancer diagnosis. During follow up; 6 (27.3%) patients died due to hematological malignancy and 16 (72.7%) patients died due to solid tumor. Thirteen (81.3%) of 16 patients who died because of solid tumor had advanced tumor. Death causes of 6 patients who died because of hematological malignancies were; 1 diffuse large B cell lymphoma, 1 peripheral T cell lymphoma, 1 AML, 1 multiple myeloma and 2 CLL.

Median interval between the diagnosis of two tumors was 11 months (95% CI: 1-168). 36 months survival was 65.5% (%95CI: 48. 0-78.4 months).

Table 3. Distribution of metachronous tumors by site (n= 25)

	NHL n (%)	HL n (%)	MM n (%)	CLL n (%)	AML n (%)	MPN n (%)	CML n (%)	Total n (%)
Lung	3 (12)	1 (4)			1 (4)	1 (4)		6 (24)
Sarcoma			1 (4)					1 (4)
Gastric adenocarcinoma	1 (4)							1 (4)
GIST	1 (4)							1 (4)
Breast	1 (4)		1 (4)	3 (12)				5 (20)
Colangiocarcinoma							1 (4)	1 (4)
CML	1 (4)							1 (4)
Larynx	1 (4)							1 (4)
Skin	1 (4)			1 (4)			1 (4)	3 (12)
Pancreas adenocarcinoma			1 (4)					1 (4)
Colon				1 (4)				1 (4)
Papillary thyroid carcinoma						1 (4)		1 (4)
Cervix			1 (4)	1 (4)				2 (8)
Total	9 (36)	1 (4)	4 (16)	6 (24)	1 (4)	2 (8)	2 (8)	25 (100)

HL= Hodgkin's lymphoma

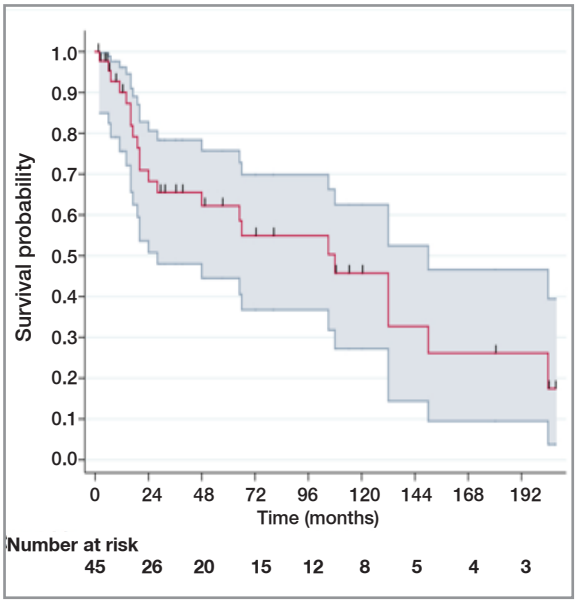

Figure 1. Survival of patients

DISCUSSION

This retrospective study has some limitations. One of these is; our study has a small patient population. Therefore we could not obtain large homogenous patients groups in our study and this was another limitation. However at the end of this study these limitations and affect of those on clinical outcomes are discussed widely with accompany of current literature.

Synchronous and/or metachronous cancers on patients with hematological malignancies are not common, yet it is believed that the incidence is increasing, and it is important to make an early diagnosis and administer prompt therapy in this situation.[4,5] The present study collected the outcomes of hematological malignancy patients with synchronous and/or metachronous tumors and analyzed the effect of the presence of secondary cancers. Among the patients, female to male ratio was 0.87:1, and the median age at first cancer diagnosis was 62 years (range 26-89 years). The more diagnosed tumors were metachronous in comparison to synchronous (25 compared with 20). Also, in our study, the most diagnosed hematological malignancy was NHL (23 cases; 51.1%), and the major histological subtypes of NHL cases were; diffuse large B cell lymphoma, peripheral T cell lymphoma, marginal zone lymphoma and follicular lymphoma. Our findings were comparable with the literature.[6,7] In a study Liu et al. analyzed 32 patients with synchronous hematologic malignancy and solid tumors, and they reported the most diagnosed hematological malignancy was NHL (18 cases; 56.2%), also the major histological subtypes were similar to ours.[6] On the other hand, while in our study, the most common site of second primary malignancy was lung (16 cases; 35.6%), in their study, the most common sites were stomach and thyroid (7 cases; 21.8% each). The difference in those results might be attributable to differences in geography, environment, race, or various diagnostic methods between studies. In our study, median follow up was 31 months (95% CI: 2-204) and the median time between the diagnosis of first cancer and death was 108 months (95% CI: 20-204). Also, while in our study, 36 months survival was 65.5% (95% CI: 48.0-78.4 months), Liu et al. reported the median overall survival in their patients was 17.7 months (range: 1.3-68 months). These results were comparable with the literature.[8,9]

In another study, Nishiwaki et al. reported the outcomes of 649 patients with hematological malignancies, including 19 patients with synchronous malignant tumors (2.9%). The most commonly diagnosed hematological malignancy was NHL (505 cases; 77.8%), and the major histological subtypes of NHL cases were similar with ours.[9] Interestingly, in that study, synchronous malignant tumors were NHL (16 cases; 84, 2%) and MM (3 cases; 15.7%), and the median follow-up period was 30 months (range, 0.6-79 months). The overall survival (OS) of patients with synchronous cancers was 77% at 2 years, and the OS of all patients was 80%. No statistically significant difference was observed between patients with and without synchronous cancers. In our study, with regard the malignancy stage of the patients both hematological and second cancers, there was no difference.

Our findings suggest that the presence of synchronous and/or metachronous cancer on patients with hematological malignancy is not a significant prognostic factor. There can be several factors those affect this result. First, less than half of our patients had advanced disease in terms of solid tumor. On

the other hand, this study has a small patient group and there are multiple combinations of cancers. Despite these, we assume that close follow-up of hematological malignancy can contribute to the early detection of another cancer. However, it will be important to treat appropriately both the hematological cancer and the concomitant solid tumor.[8] Multiple cycles of combination chemotherapy and/or radiotherapy are necessary for the treatment of hematological malignancies, such as leukemia, malignant lymphoma, and multiple myeloma.[10,11] Carcinogenic effects of those radio/chemotherapy should be considered for the synchronous and/or metachronous cancers development. On the other hand, patients with malignancy are now living longer due to advancements in therapy.[12] As a result the number of patients developing new malignancies will increase.

In order to detect second primary cancers with PET/CT, radiological and oncological findings are significant among with metabolic activity findings. Detection of the second cancer is important because it may lead to misleading results in the diagnosis of primary cancer and therefore in the treatment approach, and in terms of the treatments to be planned for the second cancer and may change the clinical approach.[13]

The role of PET-CT in second primary cancers has been emphasized in many studies, especially in head and neck cancers. However, there are not enough studies about the frequency and importance for all cancer types. In addition, with new technology devices,

CT images are applied in diagnostic quality and increasingly with intravenous contrast, allowing better characterization of lesions.[14,15]

According to guidelines, no standard treatment options are available for synchronous and/or metachronous hematological malignancies and solid tumors. The degree of malignancy of each cancer, the response of each malignancy to therapy, and the clinical condition of the patient should be considered simultaneously. A regular follow up could detect most of the second malignancies at early stage.

In conclusion, new cancers can develop at the same time or after treatment of one cancer. The incidence of second primary cancers on patients with hematological malignancies is expected to increase due to the better screening programs for early detection of malignancies as well as considerable improvement in their treatment, using novel imaging techniques and longer life expectancy. Further research may be able to identify the management of multiple malignancies.

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