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Some Patients Experience Both Chronic Lymphocytic Leukemia And A Non-Hematologic Malignancy

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SUMMARY: Cancer patients are often at increased risk for other malignancies due to shared risk factors or carcinogenecity of the treatment for prior malignancy. As survival rates for most malignancies are increasing, the number of patients with more than one malignancy is also increasing. In this report we evaluated our patients having both chronic lymphoytic leukemia (CLL) and a non-hematologic malignancy retrospectively. We had 11 patients having both CLL and a non-hematologic malignancy. We aimed to add new insights into the role of casual factors and treatment options by reporting our patients with CLL and a non-hematologic malignancy.
KEYWORDS: Chronic lymphocytic leukemia, cytogenetics, non-hematologic malignancy, risk factors

ÖZET: Kanser hastaları, ortak risk faktörleri ya da önceki malignite tedavisinin karsinojenik etkisiyle diğer maligniteler için artmış risk taşırlar. Çoğu malignite için sağkalım oranları arttığından birden fazla malignitesi olan hasta sayısı da artmaktadır. Kronik lenfositik lösemi (KLL) de solid tümör ve diğer lenfoid malignitelerin riskinde artışla birliktelik gösterir fakat bu ilişkinin mekanizması net değildir. Bu yazıda KLL ve hematolojik olmayan maligniteli hastalarımızı geriye dönük olarak değerlendirdik. Hem KLL hem de hematolojik olmayan maligniteli 11 hastamız mevcuttu. Hastaların sadece klinik ve laboratuvar özelliklerini değil sitogenetik sonuçlarını da sunduk. Amacımız bu hastalardaki nedensel faktörlerin rolüne ve tedavi seçeneklerine katkı sağlamaktır.
ANAHTAR KELİMELER: Kronik lenfositik lösemi, hematolojik olmayan malignite, risk faktörleri, sitogenetik

1. Introduction

Cancer patients are often at increased risk for other malignancies due to shared risk factors or carcinogenecity of the treatment for prior malignancy (1). As survival rates for most malignancies are increasing, the number of patients with more than one malignancy is also increasing. As chronic lymphocytic leukemia (CLL) is predominantly the disease of elderly (2), it might be preceeded or followed by other malignancies more often than other cancers (3). We suggest that reporting more patients having both CLL and a non-hematologic malignancy can add new insights into the role of casual factors and treatment options.

Case Report: Records of 11 patients known to have CLL and a non hematologic malignancy diagnosis before or after CLL are evaluated retrospectively. Sex, age at CLL diagnosis, age at non hematologic malignancy, smoking habit, time between CLL and non hematologic malignancy, survival, cytogenetics, CLL Rai stage and treatment, non hematologic malignancy type, stage and treatment are evaluated. Survival is mentioned as the time between CLL diagnosis and death. Results for the evaluated parameters are summarized in Table 1. Laboratory parameters of patients are listed in Table 2. There was no statistically significant difference between the parameters at CLL diagnosis and at non hematologic malignancy diagnosis. Immunglobulin levels were recorded only in 4 patients and none of them had hypogammaglobulinemia. Direct coombs test results were recorded in 5 of the patients. Only one patient had a positive (1+) test result without hemolysis and the other results were found negative. None of the patients died because of CLL related causes.

Table 1

Patient Characteristics

Patient no		1	2	3	4	5	6	7	8	9	10	11
Sex		Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male
Age at CLL diagnosis		74	59	62	66	67	63	69	73	59	75	56
Age at non hematologic malignancy diagnosis		67	65	64	68	67	71	80	73	60	65	57
Comorbidities		None	Hypertension	Coronary artery disease, diabetes mellitus, cerebrovascular disease	Hypertension	Diabetes mellitus	Hypertension, cholelithiasis	Diabetes mellitus, cerbrovascular disease	Hypertension, coronary artery disease	Hypertension	Hypertension, cerebrovascular disease	Hypertension
Smoking		No	No	No	No	No	No	No	No	Yes	No	Yes
Time between CLL and non hematologic malignancy (months)		88	71	20	21	Diagnosed at the same time period	96	132	Diagnosed at the same time period	15	120	11
Survival (months)		21	Not reached	105	Not reached	1	103	133	2	Not reached	Not reached	Not reached
Cytogenetics		ATM deletion 83.5%, del(13q) 83.4%	Normal karyotype	Normal karyotype	del(13q) 57.13%	Normal karyotype	Normal karyotype	Normal karyotype	Not done	ATM deletion 97.56%, del(13q) 96.33%	D13S319 deletion 83%, D13S25 deletion 70%	Normal karyotype
CLL	Rai Stage	II	I	III	II	II	II	I	II	II	0	II
	Treatment / Number of courses	Fludarabine plus cyclophosphamide / 6 courses	None	Chlorambucil / 4 courses, Fludarabine plus cyclophosphamide with rituximab / 6 courses	Chlorambucil plus methyl prednisolone / 3 courses	None	Chlorambucil plus methyl prednisolone / 12 courses	None	None	Fludarabine plus cyclophosphamide with rituximab / 6 courses	None	CHOP / 6 courses, Fludarabine plus cyclophosphamide with rituximab / 6 courses, bendamustine / 4 courses
Non hematologic malignancy	Type	Stomach adenonarcinoma	Breast invaziv ductal carcinoma	Skin squamous cell carcinoma	Breast unknown histological type	Colon adenocarcinoma	Endometrium adenocarcinoma and ovarian muscinous carcinoma	Sigmoid colon adenocarcinoma	Vagen squamous cell carcinoma	Lung squamous cell carcinoma	Breast invaziv ductal carcinoma	Lung adenocarcinoma
	Stage	$T_1N_0M_0$	$T_2N_1M_0$	$T_1N_0M_0$	$T_1N_0M_0$	$T_3N_3M_1$	IB Grade 2/IC	$T_2N_0M_0$	$T_4N_3M_1$	$T_1N_0M_0$	$T_2N_1M_0$	$T_1N_0M_0$
	Chemotherapy	No	No	No	No	No	Yes (paclitaxel, carboplatin, cyclophosphamide)	No	No	Yes (gemcitabine, cisplatin)	Yes (cisplatin, methotrexate, 5-fluorouracil with tamoxifen)	No
	Radiotherapy	No	Yes	No	No	No	No	No	No	Yes	Yes	No
	Operation	Yes	Yes	No	Yes	No	Yes	Yes	No	No	Yes	Yes

Table 2

Laboratory Parameters

Variables	At CLL diagnosis (mean±SD)	At non hematologic malignancy diagnosis (mean±SD)
Hemoglobin (g/dl)	11.6±2.18	12±2.12
White blood cell count($x10^9$/L)	99.49±112.98	27.19±112.98
Absolute Neutrophil Count($x10^9$/L)	14.31±8.08	8.64±4.28
Absolute Lymphocyte Count($x10^9$/L)	71.1±78.65	17.09±25.26
Mean Corpuscular Volume (femtolitre)	82.48±7.7	87.31±8.76
Platelet ($x10^9$/L)	293.5±118.5	254.55±167.79
Erythrocyte Sedimantation Rate(mm/h)	34.28±30.99	14.5±11.03
C Reactive Protein (mg/dl)	1.2±1.78	0.48±0.19
Beta 2 microglobulin	2.07±2.02	0.76±0.2
Immunglobulin G (mg/dl)	1172.5±532.55	624.5±195.86
Immunglobulin A (mg/dl)	212.2±90.84	45.95±34.86
Immunglobulin M (mg/dl)	61.5±45.26	23.7±20.56
Glucose (mg/dl)	115.33±20.95	138.62±78
BUN (mg/dl)	24.85±15.51	32.57±0.49
Creatinine (mg/dl)	1.15±0.49	1.32±0.87
AST (U/L)	17.66±5.53	21.85±9.83
ALT (U/L)	13.5±7.25	30.42±32.1
ALP (U/L)	489.66±456.77	258±56.65
GGT (U/L)	46.66±75.69	32.33±20.38
LDH (U/L)	631.16±448.15	407.5±130.64
Üric acid (mg/dl)	5.42±2.16	5.42±1.68
Calcium (mg/dl)	9.35±0.75	9.36±0.65
Phospor (mg/dl)	3.71±0.68	3.42±0.82
Total bilirubin (mg/dl)	0.62±10.16	0.66±0.38
Total protein (mg/dl)	6.64±0.31	6.58±0.31
Albumin (mg/dl)	3.9±0.86	4.4±0.61

CLL: Chronic Lmphocytic Leukemia, SD: Standard Deviation

2. Discussion

CLL is associated with an increased risk of developing both solid tumours and other lymphoid malignancies. Several mechanisms have been discussed for the association between CLL and second cancers including disease related and treatment related immunosuppression and shared risk factors (4). B lymphocyte defects, low gammaglobulin levels and quantitative and functional T cell defects have been documented in the setting of CLL (5). We don't know about the B and T lymphocyte defects but our patients didn't have low gammaglobulin levels and a non hematologic malignancy developed in 4 of our patients despite receiving no treatment for CLL. Environmental exposures and heritable factors of our patients were not recorded but 10 of our 11 patients were evaluated cytogenetically and del 13q and/or ATM deletion was found in 4 of 10 patients. Van den Broek et al (3) found 10% of all newly diagnosed CLL patients had a prior malignancy and cancer survivors had a 90% higher risk to be diagnosed with CLL than the general

population. The median interval between first primary malignancy and a second cancer was 3 years. Therapy for a prior cancer did not increase the risk of CLL. The short time period between CLL and non hematologic malignancy may suggest a shared common risk factor. However, the time between two diagnosis was 11-132 months in our patients and 2 patients were diagnosed simultaneously. At least two studies (6,7) found little evidence to suggest an association between treatment and subsequent development of second cancers. Chlorambucil is not very immunosuppressive. It is considered leukemogenic but this effect is particularly observed during the treatment of myeloproliferative disorders (4). However, the first line treatment of CLL is changing towards a more aggressive therapy with purine analogue/alkylator/rituximab combination. This combination is very immunosppressive (8). Chlorambucil, fludarabin, cyclophosphamide ± rituximab and CHOP (cyclophosphamide, doxorubicine, vincristine, methyl prednisolone) were the regimens our patients received before CLL diagnosis. Only 2 patients had a non hematologic malignancy diagnosis before CLL. Two or even 3 second malignancies in CLL patients have been reported with increased frequency (9). To our knowledge, neither CLL and endometrial carcinoma and ovarian carcinoma in the same patient nor CLL and vaginal carcinoma in the same patient has been reported before. Patients with CLL have an increased risk of non melanoma skin cancer (6,10,11). Patients having a high Rai stage at the time of their skin cancer diagnosis were 4.5 times more likely to develop skin cancer outcomes compared with patients having a low Rai stage (11). Our patient with skin squamous cell carcinoma received a 3 month course of chlorambucil and methyl prednisolone and was in Rai stage III. The time between two diagnosis were 20 months. The cause of death was neither CLL nor BCC in this patient. Lee et al (12) reported an incidentally identified colon cancer in a male with newly diagnosed CLL during initial staging with whole body positron emission tomography (PET) scanning with fluorine -18 fluorodeoxyglucose (^{18}F-FDG). Two of our patients had colon carcinoma one diagnosed simultaneously and the other 132 months after CLL. One was not suitable for treatment and the other refused therapy. As a result the survival after colon cancer diagnosis was only 1 month in both patients. In general, CLL is not regarded as a radiation-induced cancer (13,14). However, controversies in this issue persist (13,14). Three of our patients received radiotherapy. CLL was the first malignacy in two of them and the second malignancy only in one. Parekh et al (9) has shown that approximately 2% of patients with CLL develop lung carcinomas and 85% of the lung cancer patients were smokers. The diagnosis was made approximately 8 years after the diagnosis of CLL. Our both patients with lung cancer (one with squamous cell carcinoma and the other adeno carcinoma) were smokers but they still do well with both CLL and lung cancer. This may be due to the early stage at diagnosis. They were both diagnosed only one year after CLL diagnosis and they both received fludarabin, cyclophosphamide plus rituximab. In some previous studies, the increased risk of lung cancer was found to be independent of time since CLL diagnosis leading to the conclusion that it could not be attributed to CLL treatment (16,17). However, concomitant with the introduction of the nucleoside analogues, some studies reported increased risk of lung cancer (18-20). In conclusion, patients with CLL may also have a non hematologic malignancy. The non hematologic malignancy may occur before or after CLL diagnosis and sometimes simultaneously. This coincidence may ocur in patients who either received a chemo or radiotherapy for malignancy or not. Although the role of shared etiological factors remains unclear,

patients with CLL should be carefully evaluated in terms of non hematologic malignancy during initial staging and follow-up period. Reporting more patients having both CLL and a non-hematologic malignancy can add new insights into the role of casual factors and treatment options.

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