

## Secondary Primary Malignancy Presence and Related Factors in Chronic Lymphocytic

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### Abstract

**Objective:** The secondary primary malignancy frequencies have seen increased in chronic lymphocytic leukemia (CLL) regardless of therapy. The aim of this study was to investigate the frequency of secondary primary malignancy in patients followed with the diagnosis of chronic lymphocytic leukemia.

**Materials and Methods:** The 183 patients with diagnosed of CLL were enrolled into this study. The data of the patients were evaluated retrospectively. Patients diagnosed with CLL were categorized according to age, gender and presence or absence of additional malignancy. Patients with CLL and concomitant malignancy were compared with other patients.

**Results:** Fifty four patients (29.5%) were female and 129 (70.5%) were male. Secondary primary malignancy was detected in 9 (%4,9) patients. CD5 positivity was found in all of the patients with malignancy and in 91% of whole patients. 5.4% of males and 3.7% of females had solid organ tumors with CLL. Although the proportion of solid tumors was higher in males, this difference was not statistically significant ( $p = 0.847$ ). The mean age of cases with secondary malignancy was statistically significantly higher than that without secondary malignancy ( $p < 0.05$ ).

**Conclusion:** In our study, all of the patients with the second primary malignancy were CD5 positive. BCL2 proto-oncogene levels were found increased in CD5-positive CLL cells, not in normal B cells those were positive for CD5. In vitro studies showed that, B-CLL cells with higher BCL2 levels survive is longer than cells with lower BCL2 levels. Presence of the secondary malignancy except CLL may be related with BCL2 increment as well as CD5 positivity. We need more comprehensive studies to determine the relationship between the presence of BCL2, CD5 positivity and secondary malignancies.

**Keywords:** Chronic lymphocytic leukemia, Secondary primer malignancy

### Introduction

Chronic lymphocytic leukemia (CLL) occurs primarily in older adults, the average age of patients is approximately 70th. However, it may occasionally develop between the ages of 30-39. CLL is the most common type of leukemia in adults in Western countries, and occurrence is about 25-30% of all leukemia cases (1). Chronic lymphocytic leukemia is a B cell neoplasm, which one of the B cell chronic lymphoproliferative disorders. B cell CLL is considered a small lymphocytic lymphoma that presents differently (2), and is characterized by the accumulation of monoclonal lymphocytes with functional impairment. Although the asymptomatic phase has little effect on patients' quality of life, progression of the disease at later stages results in increased hospitalization and morbidity rates. Among the most common causes of death are systemic infections, haemorrhage, and wasting due to cachexia.

While quite rare, spontaneous clinical regression has been reported (3). The most characteristic finding of CLL is lymphocytosis in peripheral blood and bone marrow, and a persistent absolute lymphocyte count  $> 5000/\mu\text{L}$ , which is important for the diagnosis of CLL. The most common clinical findings are lymphadenopathy, splenomegaly, and hepatomegaly (4, 5). A number of retrospective studies have reported that CLL patients are at increased risk of developing other hematological and solid organ tumors. Malignancies such as lung, breast, colon, and prostate cancers have been reported to be frequently observed in non-CLL populations. The etiopathogenesis of the increase in frequency in other tumors seen in cases of CLL is as yet unclear (6, 7). In cases of CLL, the second primary tumor shows an increase in frequency independent of the treatment. In a comprehensive study, other malignancies were detected in 11% of CLL patients.

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This risk has been observed to be greater for Kaposi's sarcoma, malignant melanoma, laryngeal cancer, and lung cancer (8). In a large-scale analysis of a population of 2.3 million breast, colorectal, prostate, lung, kidney, pancreatic, and ovarian cancer patients, 19% had previously been diagnosed with CLL.

## Material and method

Our study population consisted of 183 chronic lymphocytic leukemia patients whose cases were monitored in the clinic of the Hematology Department at Yüzüncü Yıl University Faculty of Medicine Hospital (Van, Turkey) between 2010-2017. Patient files and data entered in the hospital records system were reviewed retrospectively. Patients were categorized according to age, gender, and the presence of other malignancies along with the diagnosis of CLL. Patients with other malignancies were compared to those without.

Statistical analysis: The SPSS 19.0 package program was used for statistical analysis of the data. Numerical measurements were specified as mean, maximum, and minimum, and categorical measurement as number and percentage. The independent samples T test was used to examine the relationship between categorical measurements. The level of statistical significance was .05 for all tests.

## Results

The present study included 183 patients, 54 (29.5%) women and 129 (70.5%) men. Secondary malignancy was detected in 9 (4.9%) patients, of whom two were female and seven male. The mean age of those without a secondary malignancy was 67.6 years (34 - 96) and that of those with a secondary malignancy was 75.6 years (52 - 89).

While the rate of CD5 positivity was %91 in whole study patients, this rate was %100 in patients with Secondary Malignancy. Of the patients with malignancies, esophageal cancer was detected in 3 patients, lung cancer in 3, stomach cancer in 1, skin cancer in 1, and prostate cancer in 1 patient.

In 5.4% of males and 3.7% of females solid organ tumors were present along with CLL. Although the percentage of males with solid tumors was higher, the difference was not statistically significant ( $p = .847$ ).

The mean age of cases with secondary malignancy was statistically significantly higher than those without ( $p < .05$ ) (Table I).

**Table 1.** General characteristics of all study patients

	All Patients	CLL cases without second primer malignancy	CLL cases with Secondary Primer Malignancy
<b>Number (n)</b>	183	174 (%95,1)	9 (%4,9)
<b>Age (year)</b>	68 (34-96)	67,6 (34-96)	75,6 (52-89)
<b>Gender</b>			
<b>Female</b>	54 (%29,5)	52 (%96,3)	2 (%3,7)
<b>Male</b>	129 (%70,5)	122 (%94,6)	7 (%5,4)
<b>Type of Malignancy</b>			
	Esophageal cancer		3 (%33,3)
	Lung cancer		3 (%33,3)
	Skin cancer		1 (%11,1)
	Prostate cancer		1 (%11,1)
	Gastric cancer		1 (%11,1)

## Discussion

Previous studies have determined that the most common cancers in our region (eastern Turkey) are gastric, skin, and bladder cancers in men, and esophageal, stomach, and breast cancers in women (10). In our study, the malignancies most frequently accompanying CLL were lung and esophageal cancers. The next most common malignancies were stomach, skin, and prostate cancers. One study reported other malignancies in approximately 10% of CLL patients during the course of the disease (11). In the present study, the second primary malignancy rate was 4.9%. Of the second primary malignancy cases, 22.2% were female and 77.8% were male; thus, 3.7% of the women and 5.4% of the men had a second primary tumor. Although the percentage of males with a second primary tumor was greater, the difference was not statistically significant. Some studies have determined that older age and male sex are active factors in the risk of developing new cancer in CLL cases (6). In the present study, the mean age of the patients with other malignancies (75.6) was significantly greater than the mean age of those without (67.6).

In addition, the growth of solid tumors concurrent with CLL suggests the role of possible immunological disorders (7). A total of 90% of CLL lymphocytes are of B cell origin. Although the percentages of T cells and natural killer cells do not vary, an increase in the absolute T cell count can be observed and the function of natural killer cells is diminished. B cell CLL (B-CLL) patients have a T cell subpopulation with lower levels of CD4 or CD8 than classical T lymphocytes. This may result from a nonclassical T cell developmental pathway or B cell interaction (12-15).

These types of T cells have been described in some autoimmune diseases (12). Various gene mutations have been identified that have been determined to affect tumor suppressor genes, oncogenes, DNA damage repair (ATM, TP53), RNA decay (SF3B1, DDX3X) and cell signaling pathways (NOTCH1, FBXW7), and inflammation pathways (MyD88, DDX3X, MAPK1) in CLL (16-18).

Hypogammaglobulinemia is a common finding in CLL, and, depending on the disease stage, autoimmune diseases are seen in 25% of patients, (19). Coombs positive autoimmune hemolytic anemia, immune thrombocytopenia, and pure red cell aplasia are among the autoimmune phenomena (20). Along with autoimmune diseases, the production of defective antibodies against certain infections and vaccines may also develop in CLL patients (21). In vitro studies suggest that B-CLL cells may inhibit autologous immunoglobulin production by interacting with CD95 on the surface of normal bone marrow plasma cells (22).

As discussed above, a number of nested and mostly still unexplained immunological mechanisms are among the suspected probable causes of other malignancies in CLL. BCL2 is increased not in CD5 positive normal B cells, but rather in CD5-positive CLL cells.

Furthermore, the number of lymphocytes from BCL2 lymph nodes is greater than the number of lymphocytes from peripheral blood (23). BCL2 is the only proto-oncogene known to suppress programmed cell death (apoptosis), thus prolonging cell survival (24). B-CLL cells with high levels of BCL2 survive in vitro longer than cells with lower BCL2 levels (25). Although 9% of the cases in the present study were CD5-negative, all patients with a second malignancy were found to be CD5-positive. As discussed above, this is in accordance with the increase in BCL2 in CD5-positive CLL patients. This brings the question to mind of whether it is possible that CD5 positivity carries the risk of additional malignancy for CLL patients. In future studies perhaps the subject of whether CD5 negativity has a protective role in the development of second primary malignancies will be debated.

## Conclusion

In conclusion, a second primary malignancy was more frequent in patients with chronic lymphocytic leukemia than in the normal population. The mean age of patients with a second primary malignancy was significantly higher than that of normal CLL patients. Although a second primary malignancy was more frequent in male patients, the difference was not statistically significant. All of the patients with the second primary malignancy were CD5 positive. BCL2 proto-oncogene levels were found as increased in CD5-positive CLL cells, not in normal B cells those were positive for CD5. In vitro studies showed that, B-CLL cells with higher BCL2 levels survive is longer than cells with lower BCL2 levels. Presence of the secondary malignancy except CLL may be related with BCL2 increment as well as CD5 positivity. We need more comprehensive studies to determine the relationship between the presence of BCL2, CD5 positivity and secondary malignancies.

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