

Evaluation of Second Primary Cancer Risk Among Chronic Lymphocytic Leukaemia Patients: Multicenter Study

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Abstract

Clinical course of chronic lymphocytic leukemia (CLL) is mostly indolent, much of the patients doesn't require treatment for months to years. Primary causes of death includes disease progression, second primary cancers (SPC), infections and immun deficiency (chemoteraphy and disease related). Patients with CLL have an increased risk of developing SPC and increased incidence reported in several studies. Although cytogenetic disorders and some risk factors such as ZAP 70, IGHC mutation are held responsible, there is no definitive explanation for the increased cancer risk.

Objective

The aim of this study is to determine the frequency of SPC in CLL patients and determining the relationship between these cancers and its treatment status, cytogenetic factors and other risk factors.

Materials & Methods

The study was designed as multicenter and retroprospective. The sample comprised 553 subjects with CLL diagnosis. Data collection commenced in January 2011, and completed at May 2020.

Results

Fifty-one of 553 patients followed for CLL, had a history of SPC. SPC development rate was 9.2%. The duration of CLL disease was 2.7 years on average when SPC detected. Epithelial tumors were mostly observed. According to the incidence skin, lymphoma, renal, breast, lung, gastrointestinal system, thyroid, malignant melanoma, prostate, kaposi's sarcoma, neuroendocrine tumor, ovarian, larynx and salivary gland were respectively (Table-1). The 13q deletion was the most common genetic abnormality in those who developed SPC, and the frequency of 13q deletion was found to be increased statistically significant in those with malignancy, compared to those who did not (Table-2).

Table 1. Second Primary Cancer risks of CLL patients

Solid Tumors	Observed (O)	Expected (E)	Standardized Incidence Ratio	p.value
Salivary gland	1	0.07	13.8	0.070
Melanoma of the skin	2	0,24	8.22	0,025
Kidney	5	0.69	7.25	0.001
Kaposi's sarcoma	1	0.14	7.22	0,129
Thyroid	4	0.56	7.14	0.003
Lymphoma	6	0.89	6.74	0.000
Overian	1	0.25	4	0.220
Female breast	5	1.58	3.17	0.022
Non-melanoma cancer of the skin	13	4.93	2.64	0.002
Larynx	1	0.58	1.74	0.438
Cancer of the gastrointestinal tract (stomach and colon)	4	4.22	0.95	0.609
Lung, Bronchus	5	5.62	0.89	0.661
Prostate	2	4.35	0.46	0.931

Table 2.Comparison of FISH positivity of CLL patients with or without SPC

Fluorescence in situ hybridization (FISH)	CLL patients without SPC	CLL patients with SPC	Overall	p.value
17p deletion	24/185 (12.97%)	3/24 (12.50%)	27/209 (12.91%)	0.3
11q deletion	11/97 (11.34%)	0/13 (0%)	11/110 (10%)	0.2
Trisomy 12	5/87 (5.75%)	0/12 (0%)	5/99 (5.15)	0.4
13q deletion	33/98 (33.67%)	9/16 (56.25%)	42/114 (36.84%)	0.024
ZAP70-positive	13/87 (14.94%)	0/4 (0%)	13/91 (14.28%)	0.3
CD38-positive	55/298 (18.45%)	6/21(28.57%)	61/319 (19.12%)	0.022

Conclusion

Our study emphasizes that the risk of second cancers in CLL patients is greater than the general population. In CLL patients with SPC, older age at diagnosis, 13q deletion and CD38 positivity, and treatment with fludarabine and monoclonal antibodies were found to be higher. Also we determined that SPC frequency increased independently from hemogram values, β2 microglobulin level at diagnosis, number of treatment lines and genetic mutations other than 13q, in CLL patients. In addition mortality rate was higher in CLL patients with SPC and they were prone to be in advanced stages at the time of diagnosis.

References

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