

Chronic lymphocytic leukemia and Second Primary Malignancies: A Relationship Revisited

Sir,

Chronic lymphocytic leukemia (CLL), the most commonly diagnosed leukemia globally, generally affects older persons with median survival being in excess of 10 years.^[1] Present-day treatment options achieve good responses, thereby improving long-term survival. However, not widely recognized is the fact that these patients may have rather an increased susceptibility to second primary malignancies (SPMs) among other issues.^[2] Indeed, a 20% greater risk of occurrence of any SPM has been found in studies comparing these patients to the U. S. general population. This increased risk has been seen for both solid as well as hematological malignancies.^[3] The probable causes for such observation could be genetic susceptibility, common risk factors, CLL-associated immune dysfunction, and possibly the effect of chemotherapy.

Characterization of Second Primary Malignancies in Chronic Lymphocytic Leukemia

Solid SPMs outnumber hematopoietic malignancies, as reported in different large studies. As per one of these population-based studies, lung cancer and melanoma attributed the most to the excess risk of SPMs, 59% and 31%, respectively. The highest risk of SPMs was seen within 2–5 months of CLL diagnosis, diminishing significantly after 6 months and stabilized thereafter. Even after 10 years of diagnosis of CLL, patients still had a 11% higher risk of SPMs in comparison to the U. S. general population.^[3] In a similar study of long-term CLL survivors, defined as having survived 10 years or more, nonmelanoma skin cancer was the most common SPM. Solid-organ malignancies again outnumbered hematologic malignancies with prostate, breast, lung, and cervical cancers being prominent and leukemia being the most common hematologic malignancy, translating to a cumulative frequency of 31% SPMs. Few of the predictors for the development of SPM were older age, male gender, and low platelet counts. Survival of the patients is also compromised in the patients with SPM, as reported to be 16.2 months in the above study which was in stark contrast to 22.9 years in the patients without second primary malignancy.^[4]

Putative causes of Development of Second Primary Malignancies in Chronic Lymphocytic Leukemia

1. Age: A long survival in the patients of CLL is a pointer toward age being one of the most important shared risk factors. The above two studies^[3,4] after multivariate analysis suggested the same.

2. Genetic predisposition: Aggressive genetic risk factors of CLL may predict an increased risk for second malignancies as well, as shown in a study from MD Anderson Cancer Center. Deletion 17p, 6q deletion, or 11q deletion and/or trisomy 12 conferred an increased risk in comparison to low-risk or normal cytogenetics^[5]
3. Immunodysregulation: Immunodysregulation is a known attribute of CLL with hitherto unknown mechanisms. As seen in clinical practice, deficient immunoglobulins and a predisposition to infection point to a dysfunctional adaptive immunity. T-cell repertoire is altered with a raised CD8 T-cell count and a reversal of CD4-to-CD8 ratio, present early and keeps becoming more apparent with the progression of disease^[6]
4. Effect of chemotherapy: Chemotherapeutic agents and regimens with their effect on DNA and hematopoietic stem cells may well contribute to the development of SPMs. However, risk for solid malignancies is very low in comparison to an elevated risk for hematologic malignancies^[7]
5. Others: male gender, low platelet counts, and high β 2-microglobulin levels have been found to be predictors in many retrospective studies^[3,4]

Newer Agents and Second Primary Malignancies

Bruton tyrosine kinase (Btk) inhibitors such as ibrutinib and acalabrutinib are approved now for first- as well as second-line treatment of CLL. They are believed to improve immunity in the patients of CLL.^[8,9] However, these agents are also being associated with increased risk of SPMs, particularly lung cancer and nonmelanoma skin cancer.^[10]

Screening of Chronic Lymphocytic Leukemia Survivors for Second Primary Malignancies

Given the high risk of SPMs in the CLL survivors, it is imperative to frame a clear guideline for their follow-up. Screening for nonmelanoma skin, breast, cervical, colon, and prostate cancers is recommended.^[11] Annual dermatologic skin screening is recommended for nonmelanoma skin cancer and standard screening is recommended for other cancers. A clinician should do a meticulous examination of all these patients, particularly the long-term survivors.

Conclusion

Second primary malignancies are common in the patients of CLL. Nonmelanoma skin, lung, breast, prostate, cervical, and colon cancers are the most prominent cancers in these patients. Development of a second primary malignancy

drastically reduces survival. Long-term survivors of CLL must therefore be screened for all these cancers.

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Conflicts of interest

There are no conflicts of interest.

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