Radiogenic risks of CLL – new evidence and a path for moving forward

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Abstract

One of the biggest conundrums of radiation epidemiology is whether chronic lymphocytic leukemia (CLL) is radiogenic. The radiogenic risks of CLL have an important public health implication, as it is the most common adult leukemia in the Western hemisphere (~30% of all leukemias in adults over 50.[1]) It has been known, since the early 1950's from the Japanese atomic bomb (A-bomb) survivors' study, that radiation exposure may induce most types of leukemia. However, it generally has been accepted that radiation does not induce CLL,[2,3] or closely allied small lymphocytic subtype of non-Hodgkin lymphoma (NHL).[3,4] This decision was mainly based on the first 40-years of follow-up of A-bomb survivors.[5] However, the most-recent report based on 55 years of follow-up showed a significant linear radiation dose-response.[6] It now seems clear that the major reason for the previous negative findings with regards to radiogenicity of CLL in A-bomb survivors was, most likely, due to very low incidence of CLL in the Japanese population (2-3% of all leukemia cases[7,8]).

Until recently, the majority of epidemiological studies of radiation-exposed populations, whether from occupational,[9] environmental[4] or therapeutic exposures,[10-12] also reported no excess of CLL or NHL. In a reversal of previous findings, recent cancer incidence studies from our group[13-15] and other incidence studies of occupationally exposed radiation workers[16-20] reported significantly increased radiation risks of CLL. There is now an emerging consensus on CLL radiogenicity,[21-23] but the magnitude of risks remains unknown. We have also come to understand that mortality-based studies could underestimate, possibly substantially, the occurrence of CLL due to its benign clinical course.[24,25]

The emergence of CLL as a radiation-induced disease has raised questions as to whether these cases demonstrate any unusual clinical or genetic characteristics that might differ from idiopathic CLL. We recently examined associations between bone marrow radiation doses from the Chornobyl accident and clinical manifestations of the CLL which had developed in the cleanup workers.[26] We observed that higher radiation doses and younger age at first exposure to radiation during Chornobyl cleanup work were associated with significantly shorter survival. Latent period was not associated with bone marrow radiation dose, stage of disease, chemotherapy treatment or any other clinical characteristics. In our study, the median latent period was 14 years and the median age at diagnosis was 57 years compared to the median age at diagnosis in the US of 72 years.[27]

Our group has initiated a number of genetic studies to characterize genetic complexity underlying radiogenic CLL. By comparing CLL in Chernobyl cleanup workers with CLL in males of comparable age from the general population of Ukraine unexposed to radiation, we will be able to assess somatically acquired genetic abnormalities and significantly affected pathways underlying radiogenic CLL in Chernobyl cleanup workers. Targeted sequencing using UCSF 500 Cancer Genes Sequencing Panel will identify acquired somatic mutations and characterize genetic complexity underlying radiogenic CLL.

In this presentation we will summarize the evidence to date on radiogenic risks of CLL and discuss paths for moving forward. In particular, additional clinical and genetic studies are necessary to evaluate the finding of progressively poorer survival with increasing bone marrow radiation dose to exclude effects of chance and unmeasured risk factors. Future large incidence studies are needed to characterize risks of low-dose radiation exposures[28] and to examine whether protracted and acute exposures have similar leukemogenic risks. Additional studies are necessary to better understand the differences between studies based on Cancer Registry data and on active case ascertainment.

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