BUTADIENE, CML AND THE 9:22 TRANSLOCATION: A Reality Check

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Abstract

Epidemiological studies have suggested an association between 1,3-butadiene and chronic myelogenous leukemia (CML) (Delzell et al., 2006 Health Eff Inst. [132]:1-63), a malignancy defined by the Philadelphia (Ph) chromosome (a translocation between chromosomes 9 and 22 [t(9:22)]. There are three in-frame variant forms of this translocation that will produce a functional fusion of the proto-oncogene *ABL* (chromosome 9) with the *BCR* gene (chromosome 22) to create the hybrid Bcr-Abl tyrosine kinase. ONE OF THESE FUNCTIONAL VARIANTS IS REQUIRED FOR CML; NO ADDITIONAL GENE MUTATIONS ARE NECESSARY. A corollary is that an agent that induces CML must be able to induce one of these t(9:22) translocations. Others have challenged the claim that CML is a chemotherapy-related adverse outcome in cancer patients. These latter studies demonstrated that the alkylating agents used for chemotherapy could not induce a t(9:22 translocation *in vitro* while ionizing radiation, a known inducer of CML, could, thus, leading to the conclusion that chemicals do not induce CML (Lichtman, 2008, The Oncologist 13: 645-654). Our studies have developed a system to detect, quantify and characterize the three etiologically relevant t(9:22) translocations *in vitro* in human cells (HL60) using real-time PCR. Relevant primers have been chosen, the sensitivity determined and PCR products have been sequenced to verify that the pathologically relevant translocations are those detected. A protocol has been developed to quantify t(9:22) translocation bearing cells rather than t(9:22) RNA molecules. Several quantitative studies with ionizing radiation have been conducted to demonstrate that this agent will provide a positive control for studies with butadiene and its metabolites. These radiation studies have generally provided the expected t(9:22) translocation induction by significantly increasing t(9:22) frequencies from background levels in the low 10^{-7} range to the higher 10^{-7} to 10^{-6} range. Current issues being addressed are (i) the variability that appears to be related to HL60 clones that have higher background t(9:22) frequencies and (ii) the need for better defined dosimetry data using highly sensitive NanoDot radiation detection (measurement accuracy of ±3%) to measure delivered doses of x-rays. A reliable positive control requires identification of an HL60 clone with consistently low background frequencies of spontaneous t(9:22) translocations. The protocol for studies to test the hypothesis that butadiene is etiologically related to CML will be described.