

CLINICAL UPDATE

Updates on study findings in essential therapeutic areas of cancer and blood disorders

The Association Between Breast Cancer and Lymphoma

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We reported in 2000 that lymphoma occurred in women with breast cancer more frequently than previously appreciated, and that when both diseases afflicted the same woman the lymphoma almost always was diagnosed simultaneously with or after the breast cancer.¹ That report was based on 87 patients we were able to identify with both diseases. At present, we have identified 130 patients with both neoplasms, and all conclusions initially reported are validated by analyzing the larger group of patients now available. The question, of course, is: What does the development of 2 completely different malignancies in the same patient mean?

In the same year, we published a study in which we demonstrated that approximately one third of women with breast cancer have mouse mammary tumor virus (MMTV)-like envelope (ENV) gene sequences in the DNA of their breast cancer, but not in nonmalignant tissues.² We included in that paper data on 1 patient with breast cancer and non-Hodgkin lymphoma (NHL) that had the MMTV-like ENV sequences in the DNA of both tumors. This finding was extremely interesting to us since, in addition to being considered the etiological agent of breast tumor development in inbred mice,³ MMTV, a betaretrovirus, is also considered responsible for the development of lymphoma.⁴ Subsequently, we collected paraffin blocks from other patients with both tumors and found MMTV-like ENV sequences in the breast cancer and lymphoma tissue of 6 of 12 patients studied.⁵ In addition, we have found MMTV-like ENV gene sequences in lymphomas of 3 of 19 patients diagnosed with only NHL.²

Subsequent to our earlier reports, an increasing number of case reports of patients with breast cancer and NHL have appeared, and all are simultaneous presentations of both diseases.⁶⁻¹² In addition, Tanaka et al¹³ reported that Japanese women with breast cancer had a 3.5-fold higher risk of developing NHL. However, unlike our patients who had only rarely received chemotherapy for breast cancer,¹ the increased incidence of NHL in patients studied by Tanaka et al appeared to apply primarily to patients who received chemotherapy for breast cancer.

Although still controversial,^{14,15} there is an increasing body of laboratory¹⁶⁻¹⁸ and epidemiological^{19,20} evidence that supports the hypothesis that MMTV may be important in the development of some human breast cancers and other diseases. In addition, in the mouse system there is a very close association of MMTV and lymphoid cells. The primary targets for exogenous MMTV infection in the mouse are the T and B cells located in the Peyer patches of the gastrointestinal tracts of neonatally infected pups.²¹ A very recent Russian publication reports on the detection of MMTV-like ENV gene sequences in a human mammary carcinoma patient's intestine lymphoid tissue.²² The MMTV-like retroviral sequences that have been reported in primary biliary cirrhosis patients appear to be preferentially located in lymphoid tissues with a limited viral abundance in the liver, where end organ damage occurs in this disease.²³ Similarly, human breast tumors appear to have a limited abundance of MMTV-like sequences, whereas the presence of MMTV-like sequences has been reported in human lymphocytes of breast cancer patients.^{24,25} These results argue for the ability of MMTV to infect human lymphoid tissue. If indeed such infection of human B and T cells can occur, this may not only allow for passage of MMTV to the breast but also function as an etiological agent of disease in the lymphoid tissue itself.

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Similar to the membrane proteins of bovine leukemia virus gp,^{30,26} Epstein-Barr virus LMP2A,²⁷ and Kaposi sarcoma virus K1,²⁸ MMTV's ENV gene is a membrane protein that contains immunoreceptor tyrosine-based activation motif (ITAM) domains.²⁹ Normally ITAM domains function in hematopoietic cells as ITAMs that are signaling motifs associated with activation, survival, and differentiation.³⁰ The ITAM-containing motifs of gp30, LMP2A, and K1 have been shown to be capable of cell transformation.^{31,32} Recently published data have shown that the ITAM-containing MMTV ENV protein of mice can transform both mouse and human breast tissue in vitro.²⁹ These studies implicate ITAM-containing proteins as oncoproteins. The MMTV ENV sequences that we have detected in both human breast tumors and NHL all contain this ITAM domain and should theoretically also be capable of transformation.⁵ A very curious additional finding is that all the MMTV ENV sequences that have been isolated from NHL so far studied contain an identical 1 nucleotide change at the same location with the ITAM domain. Our current goal is to determine if MMTV ITAM-containing ENV gene sequences isolated from our breast cancer and NHL patients are capable of cell transformation. If such sequences are found to be involved in transformation through signaling motifs then perhaps such a molecular mechanism could be interrupted and result in successful treatment of these malignancies.

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