Epidemiological Studies in Waldenström's Macroglobulinemia Predisposition

Ola Landgren, M.D., Ph.D., Medical Oncology Branch, NCI, NIH

BACKGROUND. A role for genetic factors in the causation of lymphoplasmacytic lymphoma/Waldenström macroglobulinemia (LPL/WM) is implicated based on prior findings from multiply affected families and small case-control and cohort studies. Furthermore, chronic immune stimulation has been associated with LPL/WM; however, available information is sparse. Recent, large, population-based studies support a role for both genetic and immune-related factors in the pathogenesis of LPL/WM.

METHODS. In the first study (*Blood 2008, 112(8)3052-6*), we identified 2144 LPL/WM patients (1539 WM [72%] and 605 LPL [28%]) diagnosed in Sweden, 8279 population-based matched controls, and linkable first-degree relatives of patients (n=6177) and controls (n =24,609). Using a marginal survival model, we calculated relative risks as measures of familial aggregation. In the second study (*J Natl Cancer Inst 2010, 102(8)557-67*), we used Swedish population-based registries to identify 2470 case patients with LPL/WM, 9698 matched control subjects, and almost 30 000 first-degree relatives of either case patients or control subjects. We evaluated a wide range of autoimmune, infectious, allergic, and inflammatory conditions. As a measure of risk, we calculated odds ratios (ORs) for each condition by use of logistic regression.

RESULTS. In the first study, we found first-degree relatives of LPL/WM patients to have 20-fold, 3.0-fold, 3.4-fold, and 5.0-fold increased risks of developing LPL/WM, non-Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), and monoclonal gammopathy of undetermined significance (MGUS), respectively. In analyses stratified by type of first-degree relative (parent, sibling, offspring), age at diagnosis of the probands (above/below 70 years), and sex of the first-degree relative, we did not observe the risk estimates to be significantly different compared with the overall analyses. In the second study, we found an increased risk of LPL/WM associated with a personal history of the following autoimmune diseases: systemic sclerosis (OR=4.7), Sjögren syndrome (OR =12.1), autoimmune hemolytic anemia (OR=24.2), polymyalgia rheumatica (OR=2.9), and giant cell arteritis (OR=8.3). An increased risk of LPL/WM was associated with a personal history of the following infectious diseases: pneumonia, septicemia, pyelonephritis, sinusitis, herpes zoster, and influenza (OR=1.4 to 3.4). Interestingly, an increased risk of LPL/WM was associated with a family history of the following autoimmune or infectious diseases: Sjögren syndrome (OR=5.0), autoimmune hemolytic anemia (OR=3.8), Guillain-Barré syndrome (OR=4.1), cytomegalovirus (OR=2.7), gingivitis and periodontitis (OR=1.9), and chronic prostatitis (OR=4.3).

Epidemiological Studies in Waldenström's Macroglobulinemia Predisposition

Ola Landgren, M.D., Ph.D., Medical Oncology Branch, NCI, NIH

CONCLUSIONS: Our findings of highly increased familial risks of developing LPL/WM, NHL, CLL, and MGUS support the operation of shared susceptibility genes that predispose to LPL/WM and other lymphoproliferative disorders. In parallel, a personal history of certain immune-related and infectious conditions was strongly associated with increased risk of LPL/WM. The association of both personal and family history of Sjögren syndrome and autoimmune hemolytic anemia with risk of LPL/WM indicates the potential for shared susceptibility (genetic, environmental, or both) for these conditions.