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Institutionen för medicin, Huddinge

Clinical prognostic markers in chronic lymphocytic leukemia

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ABSTRACT

Chronic lymphocytic leukemia (CLL) is characterized by the accumulation of mature B lymphocytes in blood, bone marrow and lymphoid tissues. The clinical course for the individual patient is still unpredictable despite decades of research on prognostic markers and staging systems. The aim of this thesis was to review the value of existing prognostic tools in order to develop new clinical prognostic markers for CLL and to assess the impact of clonal evolution and transformation in CLL in relation to biological markers and given therapy.

Paper I: This is a long-term follow-up of the first trial of subcutaneous alemtuzumab as first-line therapy in CLL. In order to assess duration of response, infectious complications and incidence of Richter transformation, a comparison was made with historical controls. Median time to treatment failure was 28 months for the alemtuzumab-treated patients compared to 17 months for the control group (not significant). Infectious complications were not more common in the alemtuzumab-treated patients despite profound and prolonged T-cell suppression. The rate of Richter transformation was similar between the groups.

Paper II: Clinical data of 77 patients included in five phase II trials at Karolinska University Hospital were analyzed to find out whether the use of computed tomography (CT) could add prognostic information to the Rai and Binet clinical staging systems. A high nodal tumor burden evaluated by CT correlated with a shorter time to next therapy and a trend towards shorter survival. Massive splenomegaly was associated with shorter overall survival and therapy-free survival.

Paper III: The expression of the estrogen receptors (ER) α, β1 and its splice variant β2 was evaluated in peripheral blood mononuclear cells (PBMC) from CLL patients and normal controls using immunocytochemistry. The expression of ERα was generally low whereas most PBMCs expressed ERβ1 in both patients and controls. ERβ2 expression was significantly more common in CLL. Patients with high expression (> 50% of PBMC) of ERβ1 and/or ERβ2 were more likely to need therapy during follow-up.

Paper IV: Paraffin-embedded splenic tissue samples were obtained from 62 patients with CLL or SLL to assess whether chromosomal aberrations in the spleen have a prognostic impact. The cytogenetic abnormalities 11q-, 13q-, 17p- and trisomy 12 were assessed by interphase FISH and compared with samples from blood and/or bone marrow. Patients with 11q- and 17p-deletions in the spleen had significantly shorter overall and therapy-free survival. Clonal evolution seemed to occur in some cases.

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