Institutionen för medicin, Huddinge

Prognostic information from nonmalignant and malignant lymphocytes in follicular lymphoma in relation to therapy

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ABSTRACT

Follicular lymphoma is the most common indolent lymphoma. It is composed of centrocytes and centroblasts, residing in follicles that also harbour nonmalignant immune and stroma cells. Follicular lymphoma is graded according to the World Health Organization criteria that are based on the frequency of centroblasts. There is consensus that grades 1 and 2 are indolent, but not whether grade 3 is aggressive. Differences between grades 3A and 3B are also unclear. The nonmalignant cells in the microenvironment interact with the tumour cells and with each other. These interactions may be important for disease outcome. Since the introduction of the therapeutic monoclonal anti-CD20 antibody rituximab, the prognosis of follicular lymphoma has improved. It is likely that the mechanisms of rituximab affect and involve not only CD20+ follicular lymphoma cells but also the surrounding as well as the systemic immune cells. The aim of this thesis was to identify biological predictors for outcome in follicular lymphoma in relation to therapy.

In paper I, using flow cytometry, we reported that higher numbers of CD8+ T cells in diagnostic lymph nodes are an independent predictor of better overall and disease-specific survival. This finding was reproduced in paper II in which computerised quantifications of tissue microarrays were used for a unifying multivariate model. This model showed that many cells in the microenvironment were independently important for outcome. Higher levels of cells positive for CD8 (cytotoxic T cells), forkhead box protein 3 (regulatory T cells) and programmed death-1 (PD-1+ T cells) correlated with good prognosis, but higher levels of cells positive for CD4 (helper T cells) and CD68 (macrophages) with poor. The best predictors for poor outcome were increasing CD4/CD8 and follicular/interfollicular CD4 ratios, suggesting that outcome is influenced by the balance between detrimental follicular B-helper and helper2 T-cells on one hand and favourable cytotoxic and helper1 T cells on the other. In paper III we used prospectively recorded flow cytometry analyses from two randomised trials where all patients received single rituximab with or without interferon-α priming. T cells in tumours (both CD4+ and CD8+) were associated with fast and good clinical responses to rituximab, while T cells in blood (both CD4+ and CD8+) correlated with slower but good and sustained responses, and were more important for survival. Interferon-α abrogated the dependence on high numbers of CD8+ cells (in both blood and tumours) for good rituximab responses. In paper IV we reviewed the follicular lymphoma grades in 828 patients with long follow-up times, of whom 40% received upfront rituximab. Compared with grade 1–3A patients and independently of clinical factors, grade 3B patients showed higher mortality but outcome was improved after upfront anthracyclines. Grade 3B patients experienced no relapses or deaths beyond five years of follow-up. Furthermore, patients with grade 3B were different in their clinical characteristics. In the entire population, patients with grade 3A had similar outcome as those with grade 1–2. However, in patients given upfront rituximab-containing therapy, increasing grades of 1, 2, and 3A correlated with better overall survival and time to treatment-failure, independently of clinical factors.

We conclude that outcome in follicular lymphoma is determined by the balance between competing immune cells in the microenvironment and by their interactions with each other and with the tumour cells. Rituximab and interferon-α alter the prognostic properties of the immune cells, and also involve systemic T cells that may be very important for disease outcome. Grade 3B, or follicular large B-cell lymphoma, is a distinct, aggressive but curable entity. Grades 1, 2 and 3A are indolent and incurable. Increasing grades predict better outcome with rituximab therapy. Our findings suggest a future of personalised therapy based on biological characteristics of the patients and of the tumours.

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