DIFFUSE LARGE B-CELL LYMPHOMA – STUDIES ON IMMUNOHISTOCHEMICAL AND CLINICAL PROGNOSTIC FACTORS

Akademisk avhandling

som för avläggande av medicine doktorsexamen vid Sahlgrenska Akademin vid Göteborgs Universitet kommer att offentligen försvaras i Sahlgrens Aula, Sahlgrenska Universitetssjukhuset, Göteborg, tisdagen den 15 december 2009 kl 09.00

av
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Avhandlingen baseras på följande delarbeten:

I. Hasselblom S, Ridell B, Nilsson-Ehle H, Andersson PO. The impact of gender, age and patient selection on prognosis and outcome in diffuse large B-cell lymphoma - a population-based study.
Leuk Lymphoma. 2007 Apr;48(4):736-45.

II. Hasselblom S, Sigurdardottir M, Hansson U, Nilsson-Ehle H, Ridell B, Andersson PO. The number of tumour-infiltrating TIA-1+ cytotoxic T cells but not FOXP3+ regulatory T cells predicts outcome in diffuse large B-cell lymphoma.
Br J Haematol. 2007 May;137(4):364-73.

III. Hasselblom S, Ridell B, Sigurdardottir M, Hansson U, Nilsson-Ehle H and Andersson PO. Low rather than high Ki-67 protein expression is an adverse prognostic factor in diffuse large B-cell lymphoma
Leuk Lymphoma. 2008 Aug;49(8):1501-9.

IV. Hasselblom S, Hansson U, Olsson M, Torén L, Nilsson-Ehle H, Andersson PO. High immunohistochemical expression of p-AKT predicts inferior survival in patients with diffuse large B-cell lymphoma treated with immunochemotherapy.
Manuscript

Göteborg 2009

University of Gothenburg

DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) – STUDIES ON IMMUNOHISTOCHEMICAL AND CLINICAL PROGNOSTIC FACTORS

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DLBCL, the most common lymphoma entity, is a potentially curable but heterogeneous disease. Most studies concerning therapy and prognostic factors have been performed on selected patient materials. It is important to identify immunohistochemical biomarkers which could add prognostic information to clinical factors. Recently, the combination of rituximab (R) and chemotherapy has resulted in improved survival, but still a proportion of patients fail to not reach sustained remission. Dysregulated apoptosis has been suggested to be involved in R-chemotherapy resistance.

The aims were to retrospectively investigate i) administered therapy, survival and clinical prognostic factors in a non-selected, population-based cohort, and for those who had received chemotherapy with curative potential, investigate the prognostic role of ii) tumour infiltrating CD3+ lymphocytes, TIA-1+ and perforin+ cytotoxic T cells (CTLs) and FOXP3+ regulatory T cells (T_{regs}), and iii) the proliferation markers Ki-67 and cyclin A, in the context of anti-apoptotic bcl-2 and galectin-3 proteins and germinal centre B-cell like (GCB) vs non-GCB phenotype (using CD10, bcl-6 and MUM-1). Finally, the aim was to investigate the prognostic role of iv) anti-apoptotic (bcl-2, MCL1, p-AKT, bcl-xL) and pro-apoptotic (Bax, Bak) proteins in patients treated with R-chemotherapy.

Out of 535 patients diagnosed between 1995 and 2000 in Western Health Care Region, only 62% accomplished chemotherapy with curative potential. The prognostic value of International Prognostic Index (IPI) was confirmed, but, surprisingly, also male sex predicted worse outcome. Immunohistochemical analysis on almost 200 patients showed that i) a small number of TIA-1+ CTLs predicted better outcome, independent of IPI and sex, but FOXP3+ T_{regs} expression was not prognostic, and ii) low Ki-67 expression, bcl-2+ and non-GCB phenotype predicted inferior survival, independent of clinical factors. The impact of Ki-67 was independent of bcl-2 and non-GCB/GCB, respectively.

In 106 patients treated with R-chemotherapy between 2005 and 2007, high p-AKT expression predicted worse survival, independent of clinical factors and bcl-2 status, a novel finding. Moreover, bcl-2 overexpression still predicted worse outcome. This suggests that p-AKT and bcl-2 overexpression could be indicators of R-chemotherapy resistance of prognostic importance.

Key words: DLBCL, sex, population-based, TIA-1, CTL, FOXP3, Ki-67, bcl-2, GCB, p-AKT.

ISBN 978-91-628-7937-2