**“focus on...” session: transformation**

**086 SNP ARRAY GENOTYPING IN 182 DIAGNOSTIC FOLLICULAR LYMPHOMA CASES IDENTIFIES SITES OF AUPD ASSOCIATED WITH OVERALL SURVIVAL AND RISK OF TRANSFORMATION**

D. O'Shea1, C. O’Riain1, F. MacDougall1, J. Gibbin1, B.D. Young1, A. Huisman1, L. Rimzi1, R. Roberts1, E.B. Smeland1, E. Campo1, J.C. Chan1, N.A. Johnson1, R.D. Gascoyne1, L.M. Staut1, T.A. Lister1, J. Fitzgibbon1

1Centre for Medical Oncology, Barts and the London School of Medicine, London, United Kingdom, 2Department of Haematology, Leukaemia Molecular Profiling Project

**Introduction:** We have previously demonstrated large-scale cryptic regions of acquired homozygosity in the form of segmental acquired uniparental disomy (aUPD) in cases of follicular lymphoma (FL). We investigated the prognostic significance of these abnormalities in a series of well characterized lymph nodes (LN) from 182 previously untreated FL.

**Methods:** SNP array analysis was performed using the Affymetrix 10K Gene-chip mapping array on DNA extracted from LN biopsies. In the absence of control normal tissue a gene set of >96% homozygosity in at least 50 contiguous SNPs was used for the detection of abnormal runs of homozygosity. Clinical data were available on 109/182 patients.

**Results:** Abnormalities (UPD and copy number changes) were detected in 105/182 (58%) patients. Sites containing regions of aUPD. Sites of recurrent aUPD were detected on 6p (25), 16p (22), 1q (17), 17p (14), 1q (6) and 8q (5). aUPD of chromosome 6p was the most common abnormality detected and included 53/105 cases. Abnormalities on 17p had a worse overall survival (p<0.01). Sites of aUPD were included the SOCS-1 and LITAF loci were predictive of transformation to high grade lymphoma (p<0.05) with 17p/21 cases transforming in the course of their disease (7 pathological, 3 clinical) versus 29/121 non UPD cases (20 pathological, 9 clinical). The number of abnormalities present at diagnosis was also predictive of outcome. 26 cases with >5 abnormalities had inferior overall survival (p=0.01) compared with 143 cases with ≤5 abnormalities on 10K SNP array.

**Conclusion:** Novel areas of aUPD occur frequently (96/182 cases, 53%) in previously untreated FL, locate on 16p, 1q21 and 16p and are associated with poor outcome. The mechanism whereby abnormalities in 16p contribute to transformation is currently under investigation.

**087 CHANGES IN FOLLICULAR LYMPHOMA ARE RELATED TO TIME TO TRANSFORMATION TO DIFFUSE LARGE B-CELL LYMPHOMA**

D. de Jong1, A.M. Leef2, M. Hautmann3, S. Heisterkamp4, M. Calaminici5, J.G. Greiner6, M. Kerst6, T.A. Lister6

1Dept. of Pathology, Netherlands Cancer Institute, Amsterdam, Netherlands, 2CRUK Medical Oncology Unit, St Bartholomew’s Hospital, London, United Kingdom, 3Dept. of Biostatistics, NKI, Amsterdam, Netherlands, 4NKI, Dept. of Pathology, Amsterdam, Netherlands, 5Histopathology, Department, St Bartholomew’s Hospital, London, United Kingdom, 6Medical Oncology, NKI, Amsterdam, Netherlands

**Background:** Gene-expression and immunohistochemical studies have provided strong evidence for the importance of the microenvironment for the clinical behaviour of follicular lymphoma (FL). Relative contributions of specific T-cell and accessory cell populations have been implicated as prognostic parameters for survival and risk for transformation. It is unknown whether the composition of the microenvironment is a stable, intrinsic property in FL or modulates over time in relation to tumor progression and transformation and would be directly predictive of adverse events.

**Methods:** Serial biopsy samples from 57 patients with indolent FL were collected from the files of both institutes. Patients were selected for complete clinical information and follow-up. Four clinical groups were defined: histological/cytological proven progression and transformation and would be directly predictive of adverse events.

**Conclusions:** The microenvironment of FL is not stable during the disease. Data suggest increased numbers of macrophages and functional disruption of FDC meshwork without physical disruption are related to imminent transformation, but irrespective of the time from diagnosis to transformation.

**088 TRANSFORMED DIFFUSE LARGE B CELL LYMPHOMAS DIFFER FROM FOLLICULAR LYMPHOMAS IN BOTH GENE AND PROTEIN EXPRESSION**

U. Andreaasson1, M. Dickor2, M. Jekterman3, R. Rosenquist4, C.A.K. Borrebæck1, S. Åk

1Department of Immunotechnology, Lund University, Lund, Sweden, 2Department of Pathology, Lund University Hospital, Lund, Sweden, 3Department of Oncology, Lund University Hospital, Lund, Sweden, 4Departments of Genetics and Pathology, Upsala University, Upsala, Sweden

**Introduction:** Follicular Lymphoma (FL), having an indolent growth pattern and a median survival of at least 10 years frequently transforms into the more aggressive Diffuse Large B Cell Lymphoma (DLBCLtr) with shorter median survival. Different genetic abnormalities have been observed upon transformation but these occur only in a subset of the DLBCLtr why it is suggested that there is no single genetic mechanism responsible for all of the transformation events. Previous studies have used complex tissue but we used sorted tumour cells to more easily study differences in gene expression rather than differences in the composition of the material.

**Material and Methods:** Gene expression analyses on highly purified FL and DLBCLtr tumour cells (sorted) were used to filter for genes significantly changed during transformation. The protein expressions were verified using immunohistochemistry on paired sets of seven pre- and post-transformation samples.

**Results:** We found 189 genes that were significantly deregulated in at least 80% of the tumours during transformation. Many of the genes are known to be associated with proliferation, but also genes not associated with increased proliferation were found to be upregulated in DLBCLtr. A number of genes were also shown to be involved in the same cellular pathways suggesting that they could contribute to the transformation by themselves, or through the pathway they are involved in. A small number of corresponding proteins were analysed using immunohistochemistry and for three of these proteins the change in protein expression were verified in 43% of seven paired biopsies pre-and post-transformation.

**Conclusions:** Using gene expression analyses on pure FL and DLBCLtr tumour samples we found genes significantly changed in the majority of the samples during transformation and we also confirmed the change in protein for three selected gene products. This suggests that the identified genes and their gene products are associated and might be involved in the molecular events during the transformation.

**089 IMPROVED PROGNOSIS AFTER HISTOLOGIC TRANSFORMATION (HT) OF FOLLICULAR LYMPHOMA (FL): THE STANFORD EXPERIENCE 1960-2003**

D. Tan1, S.A. Rosenberg1, P. Lavori2, R. Levy1, R. Hoppe1, R. Warnke4, D. Advani1, Y. Natkuunam5, A. Yuen1, S.J. Horning1

1Oncology, Stanford University, Stanford, United States, 2Health Research and Policy, and Statistics, Stanford University, Stanford, United States, 3Radiation Oncology, Stanford University, Stanford, United States, 4Pathology, Stanford University, Stanford, United States, 5Pathology, Stanford University, Stanford, United States

**Background:** HT to an aggressive lymphoma has been considered a dominant clinical event in FL, associated with brief survival. As OS has improved in both FL and aggressive lymphoma, it is of interest to determine trends in the diagnosis and outcomes of HT.

**Methods:** Among 1333 untreated grade 1 and 2 FL pt referred 1960-2003, we identified 190 pt with biopsy-proven HT, defined as diffuse large cell lymphoma (n=187) or other diffuse aggressive lymphoma (n=3). Clinical, disease and treatment characteristics were evaluated overall and according to era of FL diagnosis.

**Results:** Median age at HT was 58 yrs (27-79) and did not differ by era. Median time to HT was 4.9 yr (range: 1.23) with a 32% risk at 20 yr and no evidence of plateau. The % HT risk was higher in FL pt diagnosed >1986. Median OS after HT increased from 1.3 yr in 1960-75 era to 3.5 yrs in 1997-2003 era (p<0.004). OS at 5 yr after HT was 49% in FL pt diagnosed >1986 compared to 27% prior to 1986. Previously untreated (n=38) and rituximab-treated (n=42) pt had longer OS after HT, (both p<0.001).

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Conclusions: The prognosis for HT, which continues to be a risk throughout the course of FL, has significantly improved since 1986. Longer OS may relate to earlier recognition, improved treatment at HT, better supportive care or a combination of these and other factors.

<table>
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<th>Era</th>
<th>N</th>
<th>HT</th>
<th>Med yr to HT</th>
<th>%HT risk/yr</th>
<th>Med OS after HT</th>
<th>% HT Treated with Rtx</th>
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<tr>
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<td>3.1</td>
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<tr>
<td>1997-03</td>
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090 A RETROSPECTIVE COHORT OF LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: A LONG-TERM OUTCOME AND THE RISK OF TRANSFORMATION INTO DIFFUSE LARGE-B CELL LYMPHOMA

I. Biasoli1, A. Stamatoullas2, M. Divêce3, G. Salles4, L. Voillat5, O. Reman6, I. Biasoli1, A. Stamatoullas2, M. Divêce3, G. Salles4, L. Voillat5, O. Reman6, F. Morschhauser7, J. Audouin8, P. Brice1
1Hematologie, CHU St Louis, Paris, France, 2Hematologie, CHU-Roeun, Rouen, France, 3Hematologie, Henry-Motier, Paris, France, 4Hematologie, CHU-Lyon Sud, Lyon, France, 5Hematologie, CHU-Besançon, Besançon, France, 6Hematologie, CHU-Caen, Caen, France, 7Hematologie, CHU-Lille, Lille, France, 8Anatonie-Pathologique, Hotel-Dieu, Paris, France

Lymphocyte-predominant Hodgkin Lymphoma (LPHL) is a rare distinct disease with an associated risk of transformation into diffuse large-B cell lymphoma (DLBCL). The purposes of the present study were to analyze the overall and event-free survival and to verify the cumulative incidence of transformation into DLBCL in a large series of LPHL with a long-term follow-up.

Methods: Retrospective Cohort. The analysis of incidence of transformation was based in a high repeat biopsy rate (88%) at progression.

Results: From 1973 to 2003, 179 patients were identified. Pathologic review was done in 85% of the cases. The median age was 29 year-old (6-69), 81% were male, 83% of patients had Ann Arbor stage I-II, 67% had supradiaphragmatic disease. Forty-seven (28%) patients were treated with radiotherapy (RT), 17 (10%) were treated with chemotherapy (CT), 51 (29%) patients with combined therapy (CT and RT) and 64 (35%) were followed in a watch and wait strategy. All 115 patients treated achieved a complete remission. Among 179 patients, 67 relapsed/progressed with a median time to relapse of 3.2 years (0.3-18.2). The majority of relapses were LPHL. The median follow-up was 9.2 years. The overall survival at 10 years was 93%. The event-free survival at 10 years was 60%. Twenty-one patients progressed into DLBCL in at a median time of 4.6 years (0.41-19.6). The cumulative incidence of transformation by 10 years was 14%. Fourteen patients died (7 of progressive disease, 3 secondary cancer and 4 other causes). The cumulative incidence of secondary cancer by 10 years was 2%. The long-term follow-up of this retrospective cohort displays a favorable clinical course of this rare entity, despite frequent relapses. Also, the high biopsy rate performed at progression provides a better picture of the risk of transformation into DLBCL.

091 FREQUENCY OF TRANSFORMATION TO DIFFUSE LARGE-B-CELL LYMPHOMA IN NODULAR LYMPHOCYTE PREDOMINANT HODGKIN LYMPHOMA: THE BCCA EXPERIENCE

M.M. Almansour1, J.M. Connors1, R.D. Gascoyne1, B. Srinidhi1, K.J. Savage1
1Medical Oncology, British Columbia Cancer Agency, Vancouver, Canada

Background: Nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) accounts for approximately 5% of all HL. Although the prognosis of patients of NLPHL is typically excellent, previous observations have suggested that there is a higher risk of transformation to diffuse large B-cell lymphoma (DLBCL) than in classical HL. However, in many studies, follow-up has been limited and this event can occur years later. We evaluated the frequency of transformation in all patients diagnosed with NLPHL at the British Columbia Cancer Agency (BCCA) over a 40 y period.

Methods: The Lymphoid Cancer Database of the BCCA was searched to identify all patients with NLPHL between 1965 and 2006. 149 cases of NLPHL were identified; 4 were excluded due to composite pathology with DLBCL at diagnosis, leaving 145 cases for this analysis.

Results: Cases of NLPHL had the following characteristics at diagnosis: median age 36 y; 72% male; 70% stage I /II; 10% B symptoms; 88% normal LDH; 92% PS of 0/1. Patients with limited stage disease received radiotherapy (RT) alone (56%) or chemotherapy +/- RT (44%). Patients with advanced stage disease received MOPP-like or ABVD-like chemotherapy +/- RT. With a median follow-up of 8.2 y (1.4 y- 38 y), 15 (10%) cases of transformation to DLBCL have occurred (12 DLBCL; 2 T-cell rich B-cell lymphoma; 1 unknown). The median age at transformation was 49 y (26 y- 76 y), 13 (87%) were males, 14 (93%) had stage III/IV disease and 9 (60%) had an elevated LDH. Transformation was more likely in those with stage III/IV disease (p=0.015), B symptoms (p=0.007) or poor performance status (p=0.025) at diagnosis. The median time to transformation to DLBCL was 9.9 years (.34y to 19.6 years). The risk of transformation to DLBCL at 10 y is 7% and the projected risk at 20 y is 22%.

Conclusions: The risk of transformation in NLPHL to DLBCL is substantial and underappreciated. In this population-based study it was more often seen in patients with advanced stage, poor PS and B symptoms at diagnosis. Given that transformation can occur years after the primary diagnosis of LPHL, long-term follow-up of these individuals is necessary to accurately estimate the risk of development of secondary DLBCL.