"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

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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 patients.

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 criteria of > 96% homozygosity in at least 50 contiguous SNPs was used for the detection of abnormal runs of homozygosity. Clinical data were available on 169/182 patients.

Results: Abnormalities (UPD and copy number changes) were detected in 105/182 (58%) (range 1-6, median 2) patients, 96 cases containing regions of aUPD. Sites of recurrent aUPD were detected on 6p (25), 16p (22), 12q (17), 1p36 (14), 10p (8) and 6q (8). aUPD of chromosome 6p was the most common abnormality detected and included the MHC region (class I and II) in 23/25 cases. Patients with abnormalities of 1p36 had a worse overall survival (p=0.01). Sites of aUPD16p which included the *SOCS-1* and *LITAF* loci were predictive of transformation to high grade lymphoma (p=0.03) with 10/21 cases transforming during the course of their disease (7 pathological, 3 clinical) versus 29/121 non 16p UPD cases (20 pathological, 9 clinical). The number of abnormalities present at diagnosis was also predictive of outcome. 26 cases with >3 abnormalities had inferior overall survival (p=0.01) compared with 143 cases with ≤2 abnormalities on 10K SNP array.

Conclusion: Novel areas of aUPD occur frequently (96/182 cases, 53%) in previously untreated FL, locate to 1p, 6p, 12q 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

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Background: Gene-expression and immunohistochemical studies have provided strong evidence for the importance of the microenvironment for the clinical behavior 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 transformation to DLBCL within 3 years after first biopsy (n=11), transformation between 3 and 7 years after first biopsy (n=11), transformation later than 7 years (n=14) and no transformation with a follow-up of at least 7 years (n=21). Tissue microarrays were constructed according to standard methods (triplicate 1mm cores) and immunohistochemistry performed for proliferation, T-cell subclasses, CD68+ macrophages and CD21/CD23+ follicular dendritic meshworks. Number and location of cell populations were scored and correlated to clinical parameters.

Results: Loss of CD23 integrity of FDC networks (p=0.04) and increasing numbers of macrophages (p=0.05) were independent risk factors for transformation. T cell populations showed a variable pattern and no consistent changes related to the risk of transformation were seen.

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

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Introduction: Follicular Lymphoma (FL), having an indolent growth pattern and a median survival of about ten 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 use 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 analysis 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

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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/yr was higher in FL pt diagnosed >1986. Median OS after HT increased from 1.3 yr in 1960-75 era to 3.3 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).

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.

Era	N	HT	Med yr to HT	%HT risk/yr	Med OS after HT	% HT Treated with Rtx
1960-75	180	27	8.8	1.3	0.8	0
1976-86	426	72	6.0	1.7	1.6	4
1987-96	470	55	4.8	2.1	3.1	24
1997-03	257	36	1.9	2.8	3.3	72

090 A RETROSPECTIVE COHORT OF LYMPHOCYTE-PREDOMINANT HODGKIN LYMPHOMA: A LONG-TERM OUTCOME AND THE RISK OF TRANSFORMATION INTO DIFFUSE LARGE-B CELL LYMPHOMA

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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 (26%) 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 92%. 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

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Background: Nodular lymphocyte predominant Hodgkin Lymphoma (NLPHL) accounts for approximately 5% of all HL. Although the prognosis of patients of NPHL 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=.015), B symptoms (p=.007) or poor performance status (p=.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.