extranodal lymphoma

346 SIGNIFICANCE OF CXCR3 EXPRESSION IN GASTRIC LOW-GRADE B-CELL LYMPHOMA OF MUCOSA-ASSOCIATED LYMPHOID TISSUE TYPE FOR PREDICTING RESPONSIVENESS TO *HELICOBACTER PYLORI* ERADICATION THERAPY

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Background: Gastric MALT lymphoma is a distinct low-grade lymphoma that often regresses upon *Helicobacter pylori* eradication. The chemokine receptor CXCR3 is a candidate molecule that could influence gastric MALT lymphoma. In this study, we aimed to elucidate the correlation between CXCR3 expression and the clinicopathologic features of gastric MALT lymphoma, and to determine whether CXCR3 expression was predictive of responsiveness to *H. pylori* eradication.

Material and methods: Sixty-seven patients with gastric MALT lymphoma in a single center study were treated with *H. pylori* eradication therapy. We evaluated the correlation of CXCR3 expression with response to *H. pylori* eradication therapy by logistic regression stratified according to potential confounders.

Results: Immunohistochemical analysis revealed that 28 of 67 cases (42%) were positive for CXCR3 expression. CXCR3 expression was significantly more prevalent in those without *H. pylori* infection, advanced stage disease, and in those with *API2-MALT1* fusion. In overall analysis, those with CXCR3 expression showed a significantly increased risk of non-responsiveness to *H. pylori* eradication therapy (OR = 28.6; 95% CI, 5.70 to 143.4) compared to those without CXCR3 expression. This higher risk was observed consistently regardless of sex, *API2-MALT1* fusion, *H. pylori* infection, and clinical stage.

Conclusions: We showed that CXCR3 expression was an independent predictive factor for non-responsiveness to *H. pylori* eradication therapy in patients with gastric MALT lymphoma.

347 MICRORNA EXPRESSION IN NODAL AND EXTRANODAL DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: The aim of this project was to analyse microRNA (miRNA) expression in nodal and extranodal diffuse large B-cell lymphoma (DLBCL). Manifestation at diagnosis may be nodal and/or extranodal. At present, there are no known determinants for none of the manifestations, and no way to predict the potential progression from nodal to extranodal disease. miRNA are small regulatory RNA molecules, which function to repress/cleave sequence complementary mRNA targets. Abnormalities in miRNA genetics and expression are known to affect initiation and development of human diseases, and miRNAs are anticipated to play a direct role in oncogenesis and differentiation. Therefore, we hypothesise miRNA to be important for both characterization and progression of DLBCL.

Materials and Methods: A global miRNA screen (Exiqon miRCURY^{TM} LNA Array) of 50 snap-frozen DLBCL (40 nodal, 10 extranodal), identified differentially expressed miRNAs between the two manifestations. Subsets of miRNA profiles are pending to be validated by Taqman RT PCR assays in the original 50 snap frozen samples, 50 highly selected FFPE samples and 10 new snap-frozen samples.

Results: It was possible to distinguish between the nodal and extranodal manifestations with the global miRNA screen (e.g. mir143, mir432, mir127, and mir195). Differentially expressed miRNA target genes were predicted by target prediction software (Targetscan and Miranda). Statistically software (GOstat) to annotate target gene ontology revealed several prominent ontologies like proliferation (e.g. WNT5a, MAPK), and cell adhesion (several members of the PCDHA family) to be differentially affected in the two manifestations. Interestingly many miRNA had the wnt pathway as predicted target.

Conclusion: The two manifestations were distinct from each other with respect to miRNA expression; this difference may provide extra information about this heterogeneously disease, and lead to further studies of the differentiated miRNAs to examine the step wise progression from nodal to extranodal manifestation.

348 PRELIMINARY DATA OF A LARGE STUDY OF HIGH-RESOLUTION GENOME WIDE-DNA PROFILING IN MARGINAL ZONE LYMPHOMAS (MZL)

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Introduction: MZL subtypes (extranodal, EMZL; nodal, NMZL; splenic, SMZL) are considered unique lymphoma subtypes. Despite the fact that general clinical presentations vary and specific translocations are present only in EMZL, a high-resolution genetic analysis of these disorders has not been done.

Material and Methods: DNA from frozen biopsies analyzed with Affymetrix Human Mapping 250K arrays. Gene expression profiling with U133 plus 2.0 was performed on a subset of the cases.

Results: 38 out of 138 already collected samples have been analyzed so far: 10 NMZL, 10 EMZ, 18 SMZL. All subtypes had recurrent gains of chromosome 3, 12q13.3-q15, 14q32.33 and losses of 7q11.23, 19q13.2-pter, 19q13.2. Recurrent gains were identified in chromosome 18 (NMZL and SMZL), 1q21.3-q32.1 (EMZL), 8p23, 18q23, 20q13.33 and 21q22.3 (SMZL). Recurrent losses were identified in 7q32.1-q32.3, 14q24.2-q32.13 (SMZL), 9q34.3, 11q13.1, 16p13.3, 16p13.11 (NMZL and EMZL), 12q24.11, and 17p13.3 (NMZL). Recurrent regions of copy-neutral LOH, suggestive of uniparental disomy (UPD), were observed at 10q26.13 (SMZL), 2p21 (EMZL), and 6p21.32-p21.33 (NMZL). However, only 1/38 cases had UPD stretches longer than 5 Mb, and this was different from what we have observed in other B-cell tumors (>150), which show UPD in as many as 50% of the cases.

Conclusions: In the first series of MZL cases analyzed, in addition to known disease-specific aberrations, novel lesions have been identified. Complete data on over 150 MZL samples will be presented.

349 PROGNOSTIC SIGNIFICANCE OF PRIMARY EXTRANODAL DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) IN PATIENTS TREATED WITH R-CHOP

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Background: Previous studies in the pre-rituximab era have identified important clinical differences between nodal and primary extranodal DLBCL. We have examined the prognostic significance of primary extranodal DLBCL in the post-rituximab era.

Methods: Using the Lymphoid Cancer DATAbase of the British Columbia Cancer Agency, all patients ≥18 years of age diagnosed with DLBCL between January 1999 and May 2006 and treated with an R-CHOP regimen were included for analysis. Patients were excluded if they were HIV positive, presented with disease in the testicular or central nervous system, or had known coincident indolent lymphoma. Primary extranodal DLBCL was defined as disease confined to one or more localized extranodal sites, with no or minimal nearby nodal involvement.

Results: 513 patients were identified with the following characteristics: median age 62 y (range 19-93), male 59.1%, stage III/IV 53.8%, elevated LDH 49.5%, and performance status ≥2 38.2%. While 350 (68.2%) had at least some degree of extranodal involvement, only 133 (25.9%) had primary extranodal DLBCL. Among patients with primary extranodal disease, 70 (52.6%), 37 (27.8%) and 26 (19.6%) had 1, 2 and ≥3 extranodal sites, respectively. The most commonly involved extranodal sites included bone (33.1%), soft tissue (28.6%), stomach (15.0%), intestine (12.8%), and sinus (10.5%). Thirty-two percent, 20%, 0% and 48% of patients with primary extranodal DLBCL had stage I, II, III, and IV, respectively. This is in contrast to 11%, 34%, 26% and 29% for the nodal DLBCL group. Primary extranodal DLBCL was less commonly associated with an elevated LDH (37.6% vs. 53.7%, p=0.001). With a median follow-up of 2.8 years, no significant difference in overall survival was detected between primary extranodal and nodal DLBCL analyzed either as a group or by individual stages. Furthermore, no specific primary extranodal site confers a worse prognosis.

Conclusion: In the post-rituximab era, the previously identified survival difference in primary extranodal DLBCL is no longer observed in this large cohort.

350 IPI AND FLIPI ARE NOT APPLICABLE IN PATIENTS WITH MALT LYMPHOMA

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Background: The prognostic value of the international prognostic index (IPI) and the follicular lymphoma international prognostic index (FLIPI) has widely been demonstrated in diffuse large B-cell lymphoma and follicular lymphoma. No attempts to assess their applicability in MALT lymphoma have been performed so far.

Patients and Methods: 153 patients MALT-lymphoma were analysed. Parameters of both IPI [age>60 years, extranodal involvement ≥2, elevated LDH, PS ≥2, stage ≥3] and FLIPI [age>60 years, elevated LDH, stage ≥3, nodal involvement ≥5, hemoglobin ≤12g/dl] were assessed and correlated with relapse and time to relapse as markers of clinical course. Statistical analysis was done with SPSS 14.0. Partial correlation was assessed with the Pearson coefficient (CF) and reassessed with multiple regression analysis. Estimated time to relapse curves were calculated with the Kaplan Meier method and tested for significant differences with the Log-Rank test.

Results: According to the IPI 109 patients (71%) were classifed as low risk, 21(14%) as low-intermediate, 16(10%) as high-intermediate, and 7(5%) as high risk. FLIPI identified 100 patients (68%) at low, 33(22%) at intermediate and 14(10%) at high risk. After a median follow up time of 58 months, 132 patients are alive and 60 have relapsed (median time to relapse: 40 months). Neither IPI (CF:0.06, p=0.395) nor FLIPI (CF:0.06, p=0.4) correlated with relapse or time to relapse. Univariate analysis demonstrated stage, extragastric disease, autoimmune disease, trisomy 18 and multifocal disease as significantly correlated with relapse, while trisomy 18, extragastric disease and multifocal disease were correlated with shorter time to relapse. Multiple regression analysis identified only extragastric and mutifocal disease as predictive factors of relapse (p=0.08; p=0.011). The time of follow-up was also significantly correlated relapse (P=0.001).

Conclusion: IPI and FLIPI are not relevant for predicting the clinical course of MALT-lymphoma. Multiple regression analysis has demonstrated a significant correlation between follow-up time and relapse as well as extragastric MALT lymphoma and relapse and time to relapse. In view of this, prolonged follow-up is warranted in patients with MALT lymphoma, especially of extragastric origin.

351 CANDIDATE GENE EXPRESSION PROFILING BY REAL-TIME PCR IN FORMALIN FIXED AND PARAFFINE EMBEDDED (FFPE) SAMPLES OF PRIMARY CNS LYMPHOMAS (PCNSL)

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Background: The evaluation of biological prognostic factors in PCNSL has yielded contradictory results thus far. In this study we evaluated the feasibility of PCR based gene expression profiling using FFPE samples from immunocompetent PCNSL patients. Expression of candidate genes with prognostic impact in nodal diffuse-large B-cell lymphoma (DLBCL) was correlated to survival in PCNSL.

Methods and Material: FFPE tumor samples from PCNSL patients obtained by open resection were collected, and samples with a tumor content of >70% were subjected to RNA analysis. RNA was extracted using commercially available kits and reverse transcribed with sequence specific primers. The expression of BCL2, BCL6, CCL3, CCND2, HGAL, FN1, MYC, MUM1, LRMP, PLAU and IL4 was measured and normalized to the mean expression of four endogenous control genes: GAPDH, GUSB, PKG1, SDHA. Overall survival (OAS) was determined using the Kaplan-Meier method and the prognostic impact of gene expression using the Cox model.

Results: Samples from 42 patients with PCNSL, all histologically DLBCL, and a median age of 63 (26-87) years were evaluated. All patients have been initially treated with high-dose (4g/m^2) methotrexate, followed by a consolidating and rescue whole brain irradiation in 10 patients each. RNA could be extracted from all samples. Electrophoretic quality control identified considerable RNA degradation. Except for IL4, the expression of all genes could be measured in 40 samples (95%). The median OAS of all patients was 29 (0.5-69) months. None of the genes examined had a statistically significant influence on survival, however, a trend towards longer survival was seen for the overexpression of FN1 (HR 1.35, p=0.09), and PLAU (HR 1.27, p=0.17), and the reduced expression of CCND2 (HR 0.87, p=0.19). Patients <60 years had a median OAS of 32 months compared to 24 months for older patients (p=0.3). Karnofsky index had no impact on survival.

Conclusion: FFPE material is suitable for RT-PCR based analysis of genes with possible prognostic impact in PCNSL. However, the results obtained yielded no statistical significance. This might be due to their inability to predict clinical outcome in PCNSL or to the relatively small cohort investigated.

352 THE ROLE OF RADIOTHERAPY, PERFORMANCE STATUS, AND DOSAGE OF METHOTREXATE ACCORDING TO THEAGEIN PRIMARY CNS LYMPHOMA PATIENTS RECEIVED UPFRONT HIGH DOSE METHOTREXATE BASED CHEMOTHERAPY

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Introduction: We evaluated the role of RTx after CTx, initial performance status, and total cumulated dosage of MTX according to the age in PCNSL.

Material and methods: 188 immunocompetent PCNSL patients (median age 50 years) receiving CTx containing high-dose MTX (>1 g/m2) were selected at 17 institutions.

Results: Age≤50 years, ECOG<2 and RTx after CTx were significant prognostic factors predicting improved OS. Multivariate analysis indicated that ECOG<2 (P=0.044, OR=1.76) and RTx after CTx (P=0.001, OR=2.69) were significant prognostic factors for prediction of OS. Planned treatment was CTx alone (group1) in 64 (34%, median age 61 years) patients and CTx followed by RTx (group2) in 124 (66%, median age 46 years). Among the patients≤50, group2 patients survived longer than group1 (3-years OS; 79% vs 56%, P=0.03). Other risk factors were not statistically significant. Adding cytarabine to MTX based CTx, combination MTX based CTx, and adding intrathecal CTx did not improved OS in the PCNSL patients≤50. Multivariate analysis indicated that higher total cumulated dosage of MTX (≥5 g/m2) (P=0.041) was significant prognostic factor for prediction of OS in the PCNSL patients≤50. Among the patients>50, group 2 patients also survived longer than group 1 (3-years OS; 73% vs 39%, P=0.01). ECOG<2 was significant prognostic factor for prediction of OS (P=0.03). Other factors including total dose of MTX were not significant.

Conclusions: In the younger PCNSL patients, CTx followed by RTx improved survival and sufficient total cumulated dosage of MTX or combination MTX based CTx regimen might improve the OS. In elderly PCNSL patients, initial ECOG was the important factor for predicting OS.

353 THE NF-κB PATHWAY AS A TARGET TO INCREASE APOPTOSIS IN PRIMARY MEDIASTINAL B-CELL LYMPHOMA (PMBL): STUDIES WITH SMALL MOLECULE IKK INHIBITOR ML120B, BORTEZOMIB (BTZ), CYCLOPHOSPHAMIDE (CY) AND COMBINATION THERAPY

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PMBL is a rare subtype of diffuse large B-cell lymphoma (DLBCL) with a significantly lower EFS than other identically treated DLBCLs (Lones/Cairo, JCO, 2000). Upregulation of anti-apoptotic NF-kB pathway genes occurs in PMBL (Rosenwald, J Exp Med, 2003). We studied the effect of 2 NF-kB pathway blocking agents, BTZ and ML120B (supplied by Millennium Pharm, MA), and Cy on apoptosis in PMBL to identify strategies to increase cell death.

PMBL line Karpas-1106P was incubated with ML120B (10 μg/ml), BTZ (5 ng/ml), Cy (1.25 mg/ml), ML120B+BTZ or ML120B+Cy for 24h. Percentage of cells induced to undergo apoptosis was measured using Annexin V-FITC. DLBCL line SUDHL-6, with low expression of NF-kB genes, was used for comparison. For combination studies, comparisons were made between single and combination therapy samples run simultaneously.

Significant increases in PMBL apoptosis occurred after incubation with each agent (ML120B: 4.0%±1.13, p<.0005; BTZ: 5.25%±1.43, p<.02; Cy: 4.8%±1.05, p=.006). Significant increases occurred in SUDHL-6 after treatment with BTZ (46.42%±6.52, p<.0001), but not after treatment with Cy or ML120B. ML120B+BTZ led to a synergistic increase in apoptosis in PMBL when compared to ML120B single agent therapy (17-fold [1700%] increase, p<.01) and BTZ single agent therapy (4-fold [400%] increase, p<.01), respectively. In contrast, ML120B+BTZ did not cause an increase in apoptosis in SUDHL-6, with no significant change in apoptosis found after treatment with ML120B+BTZ vs. BTZ alone (BTZ: 25.92%±1.32, ML120B+BTZ: 24.62%±5.19, difference in increase between BTZ & BTZ+ML120B: 1.29%, p=NS). ML120B+Cy in PMBL led to an additive increase in apoptosis (ML120B: 5.49%±1.74, Cy: 6.57%±1.16, ML120B+Cy: 13.82%±2.3, p<.03).

ML120B and BTZ both increase apoptosis in PMBL, possibly by blocking the NF-kB pathway at different points. This may explain why combination therapy with ML120B+BTZ is synergistic, while the effect of ML120B+Cy is additive. Studies to assess expression of NF-kB genes in PMBL after single and combination therapy are underway.

354 ADDITION OF RITUXIMAB TO CHOP GREATLY IMPROVES THE OUTCOME OF PATIENTS WITH PRIMARY MEDIASTINAL LARGE B-CELL LYMPHOMA (PMLBCL)

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Background: Rituximab-CHOP (RCHOP) is superior to CHOP, being the new standard of care for patients with diffuse LBCL. In PMLBCL, which usually affects young patients, several investigators prefer the use of MACOP-B or even front-line high dose therapy with autologous stem cell support (HDT-ASCT). However, the role of RCHOP in PMLBCL is not well established yet.

Patients and Methods: 82 patients with PMLBCL were treated in 6 centers (1994-2007): 39 consecutive patients who received RCHOP±Radiotherapy (RT) were compared to 43 consecutive historical controls, who had received CHOP±RT.

Results: The median age of the patients was 31 years (17-82) and 53/82 (65%) were females. All individual IPI parameters and B-symptoms were balanced between the two groups. The median follow-up of currently alive patients was 33 and 88 months for patients treated with RCHOP±RT and CHOP±RT respectively. All failures occurred within 22 months from diagnosis. The 3-year failure free survival (FFS) was 81±6% vs 53±8% for patients who received RCHOP±RTvsCHOP±RT (p=0.006). The 3-year event free survival (EFS) was 79±7% vs 51±8% (p=0.007). The 3-year overall survival was 92±5% vs 67±7% (p=0.009), while the 3-year lymphoma specific survival (LSS) was 94±4% vs 67±7% (p=0.003).

Conclusions: RCHOP±RT provided very good results in PMLBCL: Early progressions were minimized, long-term FFS exceeded 80%, and only 3 lymphoma-related deaths were recorded so far in 39 patients after a median follow-up of 33 months. Patients treated with RCHOP had significantly higher FFS, EFS, OS, and LSS, when compared to CHOP-treated historical controls. Based on these results we continue to treat PMLBCL patients with RCHOP±RT, avoiding more intensive strategies.

355 NO BENEFIT OF ADDING RITUXIMAB TO CHOP REGIMEN IN PATIENTS WITH PRIMARY EXTRANODAL TYPE OF DIFFUSE LARGE B-CELL LYMPHOMA

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Background: The addition of rituximab to CHOP chemotherapy (R-CHOP) has significantly improved clinical outcome for patients (pts) with diffuse large B-cell lymphoma (DLBCL). However, new predictors of response to R-CHOP have not been established. We performed a retrospective analysis to evaluate the clinical impact of R-CHOP and tried to identify clinical predictors to get better benefit from R-CHOP compared with CHOP in pts with DLBCL.

Material and methods: Using the population-based cancer registry for non-Hodgkin's lymphoma of Asan Medical Center, we identified eligible 177 pts who were newly diagnosed with CD20-positive DLBCL and treated with CHOP (n=82) or R-CHOP (n=95) as first-line therapy from January 2001 to November 2005. We especially subgrouped all pts into either primary extranodal lymphoma (PENL, n=72) or nodal lymphoma (NL, n=105) according to the main origin of disease. PENL was defined as lymphoma which had either no or minor nodal involvement along with a clinically dominant extranodal component after routine staging procedures. Response rate, event-free survival (EFS) and overall survival (OS) were compared between CHOP and R-CHOP group. To identify clinical predictors, subgroup analysis was performed with log-rank test and Cox regression model.

Results: Complete response rate and overall response rate were higher in R-CHOP than CHOP group though it didn't meet statistical significance between two groups (79% vs 69%, p=0.16 and 97% vs 90%, p=0.07). Two-year EFS and OS rates were higher in R-CHOP group (82% vs 74%, p=0.22 and 83% vs 77%, p=0.23). In subgroup analysis, pts with NL had a prominent survival benefit from R-CHOP over CHOP (p=0.02 in EFS and p=0.03 in OS) but pts with PENL did not (p=0.37 in EFS and p=0.61 in OS). Other factors such as age, ECOG performance status, stage, LDH and IPI showed no difference for survival outcome according to treatment regimen.

Conclusions: R-CHOP regimen showed improved outcome in pts with DLBCL compared with CHOP, but pts with PENL had no benefit from addition of rituximab to CHOP chemotherapy. These pts might need other treatment strategy.

356 ANTI-TUMOR ACTIVITY OF BLIND DOXYCYCLINE IN LOCALIZED OCULAR ADNEXAL MUCOSA-ASSOCIATED LYMPHOID TISSUE (MALT) LYMPHOMA

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Introduction: Despite a variable association between ocular adnexal MALT lymphoma and *Chlamydia psittaci* (Cp) infection, high rate of Cp-positivity was observed in Korean patients with ocular adnexal MALT lymphoma. Additionally, there are conflicting results regarding Cp-eradicating doxycycline. This study was undertaken to analyze the efficacy of blind doxycycline in localized ocular adnexal MALT lymphoma.

Materials and methods: Twenty-one patients diagnosed as extranodal marginal zone B-cell lymphoma of MALT type were analyzed. Doxycycline at a dose of 200mg daily for 3 weeks was given to unselected patients with ocular adnexal MALT lymphoma as a first-line (n=17) or second-line (n=4) between 2005 and 2007. Lymphoma response and progression-free survival (PFS) were analyzed.

Results: Patients' median age was 47 with a male-to-female ratio of 0.6:1. Doxycycline was well-tolerated in ocular adnexal lymphoma patients, of whom only one discontinued doxycycline after one week due to dizziness. Seven patients (33%) achieved lymphoma regression (2 complete responses and 5 minimal responses), while remaining 14 patients showed stable disease. In the first-line group, two-year PFS rate was 65% and median PFS was 22.2 months. In patients with disease progression, subsequent chemotherapy or radiotherapy induced complete response in 4 out of 6 patients. However, in the second-line group, two-year PFS rate was 50% and median PFS was 10.5 months. Overall, 13 (62%) of 21 patients remained progression-free after doxycycline therapy after a median follow-up of 18 months.

Conclusions: Doxycycline alone is effective in localized ocular adnexal MALT lymphoma as a first-line treatment. Future efforts should be directed toward determining the Cp status and finding a marker associated with doxycycline resistance.

357 CHLAMYDOPHILA PSITTACI *(CP)* IS VIABLE AND INFECTIOUS IN THE CONJUNCTIVA AND PERIPHERAL BLOOD OF PATIENTS WITH OCULAR ADNEXAL MALT LYMPHOMA (OAML): RESULTS OF A PROSPECTIVE TRIAL

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Background: Some lymphomas are linked to specific bacterial infections. Confirmation of these associations by bacteria isolation from patients' (pts) samples (second Koch's postulate) has been achieved for *H. pylori*, but not for other lymphoma-related bacteria. OAML is linked to *Cp*infection, but the viability and infectivity of this microorganism in OAML pts has not been investigated yet.

Methods: A single-center prospective trial was conducted to assess the prevalence of *Cp* infection in 20 OAML pts and 42 healthy blood donors referred to our Institution in a 6-month period, and to define whether the *Cp* DNA and antigens previously detected in OAML pts correspond to a viable and infectious microorganism. The presence of *Cp* on conjunctival swabs and peripheral blood mononuclear cells (PBMC) of pts and donors was assessed by TETR-PCR and *in vitro* cultural methods. The presence of *Cp* was assessed also in lymphoma tissue.

Results: Donors were more commonly young males living in urban areas, whereas OAML pts frequently reported a history of chronic conjunctivitis and prolonged contact with household animals (85% vs. 38% of donors; p=0.00001). *Cp* was detected in lymphoma tissue of 15 (75%) pts. *Cp* DNA was detected in conjunctival swabs and/or PBMC from 10 (50%) OAML patients and in PBMC from one (2%) donor (p=0.01). Viability and infectivity of *Cp*, demonstrated by growth in cell cultures, were confirmed in conjunctival swabs and/or PBMC from 5 (25%) OAML pts, but not in donors (p=0.002).

Conclusions: This prospective trial demonstrates, for the first time, that *Cp* is viable and infectious in conjunctival swabs and/or PBMC of OAML pts. *Cp* infection is common in OAML pts and exceptional in blood donors. Epidemiological features in OAML pts are consistent with increased risk of *Cp* exposure.

358 VALUE OF ^{18}F-FDG-PET SCAN IN THE DIAGNOSIS AND STAGING OF OCULAR ADNEXAL LYMPHOMA (OAL): A LARGE SINGLE CENTRE EXPERIENCE

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Introduction: Fluorine 18 deoxyglucose Positron Emission Tomography (PET) is largely used in the staging of non-Hodgkin's lymphomas (NHL), but very few studies have focused on its role in the initial staging of patients (pts) presenting ocular adnexal lymphoma (OAL). The aim of this study was therefore to evaluate the role of FDG-PET in the diagnosis of ophthalmologic lymphomatous localizations.

Patients and Methods: A retrospective review of all imaging records, including computed tomography (CT), magnetic resonance imaging (MRI), and ^{18}F-FDG-PET of all OAL pts treated at the Institut Curie between 2003 and 2007 was performed. The ability of PET studies to detect lymphomatous ophthalmologic involvement was then compared with other staging explorations.

Results: Thirty-one OAL pts were included in the study. Pathological review according to the WHO classification showed 22 low-grade lymphoma pts (71%) in whom 15 MALT lymphoma (48%) and 9 high-grade NHL in whom 6 diffuse large B-cell lymphoma (19%). Ophthalmologic sites were intra-orbital in 20 pts (65%) in whom 3 with bilateral localizations and conjunctival in 14 pts (45%) in whom 3 with bilateral localizations. All patients had FDG PET and orbital MRI assessment at diagnosis in 21 cases and orbital CT in 28 pts. ^{18}F-FDG PET positive lesions were correlated to pathological sites detected by MRI in 12/21 pts (57%) and 6 pts had negative FDG PET but positive MRI;^{18}F-FDG PET positivity was correlated to pathological sites detected by CT in 17/28 pts (61%). At last, concordances between PET/MRI and PET/CT were 71% (p=0.06) and 79% (p=0.02), respectively. The sensitivity of FDG PET, MRI, and CT were 77%, 87%, and 80%, respectively.

Conclusions: As anticipated, this study shows that ^{18}F-FDG-PET has a lower sensitivity than MRI to detect ophthalmologic lymphomatous localizations.

359 PROGNOSTIC VALUE EXPRESSION OF CD38 IN PRIMARY GASTRIC MALT-LYMPHOMAS

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Background: B-cell lymphomas of mucosa-associated lymphoid tissue (MALT) represent a clinically, morphologically and biologically heterogeneous group. There is no information about prognostic value expression of CD38 in MALT-lymphomas. The aim of our study was to evaluate the level of expression CD38 and outcome of patients with primary gastric MALT-lymphomas.

Materials: We have studied immunohistological features of 34 pts with primary gastric MALT-lymphomas stage I (Lugano) treated between 1995-2005. There were 15 (44%) males and 19 (56%) females. Age of patients (pts) ranged 21-79 years (median 58). The median of follow-up was 36 months (range 3-96). Two groups were identified. First group (3 pts) - expression of CD38 on lymphoma cells, second group (31 pts) - expression of CD38 on plasmocytes. Last group may be subdivided in two groups: 12 (39%) pts with low level of CD38+ plasma cells (group A) and 19 (61%) pts with intensive CD38+ plasma cell reaction (group B). Helicobacter pylori infection status was assessed as positive in 31 cases. Antibacterial treatment was performed for 31 patients with expression of CD38 on plasmacytes. Three patients with expression of CD38 on lymphoma cells were treated by chemotherapy.

Results: Results were analysed in group A and B. Complete remission was observed in 93%. Eight (27%) pts had relapses: 6 relapses were mainly in group B, only 2 in group A. The 2-years disease free survival was 86% in pts with low level of CD38+ plasma cell, 53% in pts with intensive CD38+ plasma cell reaction (not significant).

Conclusions: The present results show that the cases of primary gastric MALT-lymphomas stage I (Lugano) with different level of CD38+ plasma cell in lymphoma tissue have various clinical outcome, long-term survival and risk for relapses. These results could be taken into account for the individual treatment for patients with primary gastric MALT-lymphomas with initial high CD38+ plasma cell proportion. Future studies of expression CD38 may be helpful for assessment of prognosis for patients with gastric MALT-lymphomas.

360 INFLUENCE OF TP53 MUTATIONS ON GENOMIC INSTABILITY AND EXPRESSION PROFILES IN 22 DIFFUSE LARGE B CELL LYMPHOMAS OF THE GASTROINTESTINAL (GI)-TRACT

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Introduction: *TP53* is regarded as one of the main tumor suppressors. Deletion and/or mutations of *TP53* are believed to cause genomic instability and neoplastic transformation and progression.

Material and methods: Twenty-two diffuse large B cell lymphomas of the GI-tract were analyzed for deletion and mutations of the *TP53* by FISH and sequencing. The data were correlated with a database that integrated genomic abberrations detected by CGH/FISH and data from expression profiling of microdissected lymphoma cells of a cDNA chip containing 2300 genes. Feature class selection for isolation of new prognostic genes was performed. TP53 protein and proliferation index were evaluated by immunohistochemistry.

Results: In 7/22 lymphomas a deletion (5/22) or a mutation (5/22) of *TP53* was detected. When compared to the numbers of genomic aberrations no correlation regarding a higher number of aberrations was detected. More than two cytogenetic aberrations were correlated with significantly shorter mean survival, while *TP53* failed as a predictor. Genomic profiling of deleted and mutated *TP53* lymphomas revealed four differentially expressed genes in both groups (false discovery rates 0.003 and 0.006, respectively). These were PTPRD, which is an analogue of CD45; CCNG2, a cell cycle regulator; MAPK12, a major transducer of extracellular signals; and CCL7, a monocyte chemotactic protein. Nuclear TP53 protein accumulation was generally low in the deleted cases while TP53 was heterogeneously detected in the mutated lymphomas ranging from 5% to 95% positive lymphoma cells.

Conclusions: A core group of four differentially expressed genes was defined that might be influenced by mutations/deletions of *TP53*. Furthermore, feature selection for class selection of complete remission revealed a group of differentially expressed genes of prognostic value.

361 CLINICOPATHOLOGICAL FEATURES AND OUTCOME OF STAGE I GASTRIC MALT LYMPHOMA TREATED WITH ANTI-*HELICOBACTER* THERAPY

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Background: The efficacy of Helicobacter Pylori (HP) eradication in localized gastric MALT lymphoma is well established with remission rates between 60-100% of cases. However, only scanty information is available about long-term follow-up of antibiotic-treated cases.

Methods: 100 patients (pts) with stage I gastric MALT lymphoma were treated initially with anti-HP eradication regimens comprising antibiotics in association with proton-pump inhibitors. Follow-up endoscopies with multiple biopses were carried out at 6 months intervals.

Results: Median age at diagnosis was 64 years. All patients presented with gastrointestinal symptoms (mainly abdominal pain/dyspepsia) but no B symptoms were observed. HP was detected by histology in 80%. Lymphoma was most often localized in the antrum (30%), was multifocal in 19%, associated with gastritis in 54% and with ulcers in 29% of cases. After antibiotics, HP was eradicated in all positive patients (19 of them after a second line of antibiotics). Symptoms disappeared and macroscopic findings improved in almost all patients. Lymphoma regression was achieved in 78 of 97 evaluable patients (80%, 95% CI.: 71-88%) with histological complete remission (CR) in 66 (Wotherspoon's score 0-2) and partial remission (score 3) in 12 pts. A multifocal presentation was significantly (p=0.04) associated with lower CR rate (47%) in comparison with fundus+ body (65%) and antrum (82%). The median follow-up time was 6.5 years; 34 of the 78 responders showed continuous histological remission, while 33 had histological score fluctuations (from 0-4) and 11 pts had a frank lymphoma relapse (2 with high-grade trasformation). The 5-year and 10-year overall survivall rates were 91% (95% CI, 83-95) and 82% (95% CI, 69-90), respectively.

Conclusions: Hp eradication therapy resulted in CR in the majority of cases, with a significantly higher CR rate in tumors of the distal stomach. Long-term clinical disease control was achieved in most cases. Incidence of histologic transformation seems lower in gastric MALT lymphoma than in other low-grade lymphomas.

362 INTRAVASCULAR LARGE B-CELL LYMPHOMA (IVLBCL): INTERNATIONAL CONSENSUS ON DIAGNOSTIC AND THERAPEUTIC ISSUES

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Background: IVLBCL is a rare form of diffuse large B-cell lymphoma with preferential intravascular growth of malignant lymphocytes, aggressive behavior, and usually fatal course. IVLBCL often affects elderly patients with poor PS, elevated LDH serum levels, anemia, and B-symptoms, with possible differences in clinical presentation between cases diagnosed in Western Countries and Japan. Many characteristics of IVLBCL are poorly known and may be broader than those currently described.

Methods: On behalf of the International Extranodal Lymphoma Study Group, clinicians and pathologists interested in IVLBCL, coming from Western and Eastern countries, joined to reach a consensus on the most urgent unresolved issues in IVLBCL: to this end, a representative group of IVLBCL cases coming from Western countries

and Japan were collectively analyzed. IVLBCL features were proposed both under clinical and pathologic standpoints.

Results: the consensus indicated that: IVLBCL have additional morphological criteria including definition of affected vessels, cell size (somewhat smaller cell may occur), peculiar sites of involvement (kidney, spleen and liver), and immunophenotype (in particular CD5 expression); difference in clinical forms of IVLBCL is driven more by the presence of haemophagocytosis rather than geographical origin of patients; "cutaneous variant", PS, stage, and therapeutic modality are independent prognostic variables; therapy is improved by anthracycline-based chemotherapy plus rituximab, CNS prophylaxis and consolidation with high-dose chemotherapy supported by autologous stem cell transplant, mostly in high-risk and young patients.

Conclusion: IVLBCL is a peculiar type of diffuse large B-cell lymphoma under pathological, immunophenotypic, clinical and therapeutical standpoints. An international prospective protocol, aimed to study both therapeutical and biological features of this disease is currently being designed.

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363 RITUXIMAB IMPROVES OUTCOME IN WESTERN PATIENTS WITH INTRAVASCULAR LARGE B-CELL LYMPHOMA (IVL)

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Background: The addition of rituximab to anthracycline-containing chemotherapy has significantly improved outcome in patients (pts) with diffuse large B-cell lymphomas. The impact of this monoclonal antibody in IVL, a rare variant of diffuse large B-cell lymphoma characterised by the growth of neoplastic cells into small blood vessels was recently explored in a large series of Japanese pts, while experience in IVL pts diagnosed in Western Countries is limited to a few case reports

Methods: The impact of the addition of rituximab was evaluated in 28 pts affected by CD20+ IVL eligible for CHOP/CHOP-like regimen: 8 pts were treated with rituximab +chemotherapy (R-CT) and 20 with chemotherapy alone (CT).

Results: Median age was 67 yrs (range 39-86; 15 males). 75% of pts had an IPI≥3. B symptoms, PS≥3, increased LDH levels, and stage IV were respectively observed in 78%, 41%, 88%, and 71% of cases. Skin (44%), CNS (30%) and bone marrow (30%) were the most common sites. Laboratory tests revealed: anemia (78%), leucopenia (30%), thrombocytopenia (37%), and increased LDH (88%). No significant differences between R-CT and CT groups were observed. Overall, 18 (64%) pts achieved complete remission (CR), and 2 partial response with an early progression (PD), 6 (21%) experienced a PD, and 2, both in CT group, died of toxicity. Noteworthy CR was obtained in 100% of R-CT versus 50% of CT pts (p=0.03); the addition of rituximab was related to CRR. At a median f-up of 14 mo, all 8 R-CT pts are alive and relapse free; at a median f-up of 71 mo, only 7 CT pts are alive and disease-free. The 3-yr EFS was 35% in CT group and 100% for R-CT pts (p<0.0001); the 3-yr OS was 39% and 100%, respectively (p<0.0001).

Conclusions: the addition of rituximab to anthracycline-based chemotherapy significantly improves outcome in IVL pts diagnosed in Western Countries. A confirmatory international prospective trials is warranted.

On behalf of the International Extranodal Lymphoma Study Group (IELSG)

364 A RETROSPECTIVE ANALYSIS OF RITUXIMAB-CONTAINING CHEMOTHERAPIES FOR INTRAVASCULAR LARGE B-CELL LYMPHOMA

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Background: Intravascular large B-cell lymphoma (IVL) is a rare subtype of extranodal diffuse large B-cell lymphoma (DLBCL) with poor prognosis. Addition of rituximab to CHOP and CHOP-like regimens has been found to improve the outcome of DLBCL. However, the efficacy of rituximab in IVL remains unclear.

Objective and Patients: To evaluate the usefulness of rituximab in IVL, we retrospectively analyzed 106 patients (59 men, 47 women) with IVL who received chemotherapy either with rituximab (R-chemo, n=49) or without rituximab (Chemo, n=57) between 1994 and 2007 in Japan. Median patient age was 67 years (range, 34 to 84 years). IPI was H-I/H in 97% of patients.

Results: Complete response rate was higher for R-chemo (82%) than for Chemo (51%, *P*=0.001). Median duration of follow-up for surviving patients was 18 months (range, 1 to 95 months). Progression-free survival (PFS) and overall survival (OS) rates at 2 years after diagnosis were significantly higher for R-chemo (PFS: 56%; OS: 66%) than for Chemo (PFS: 27%, *P*=0.001; OS: 46%, *P*=0.01). Multivariate analysis revealed use of rituximab was favorably associated with PFS (HR, 0.45; 95% CI, 0.25 to 0.80; P=0.006) and OS (HR, 0.42; 95% CI, 0.21 to 0.85; *P*=0.016). Adverse events related to rituximab infusion were observed in 14 of 49 patients (29%). Grade 3 hypoxia due to rituximab infusion was observed in one of 49 patients (2%). Treatment-related death was observed in 3 patients (6%) with R-chemo and 5 patients (9%) with Chemo. Twelve of 49 patients (24%) in the R-chemo group and 31 of 57 patients (54%) in the Chemo group had died as of final follow-up. In the R-chemo group, 4 patients each died of progressive disease (PD) and relapsed disease (RD), respectively. In the Chemo group, 15 patients and 11 patients died of PD and RD, respectively.

Conclusion: Our data suggest improved clinical outcomes for patients with IVL in the rituximab era without significant increase in toxicities. Future prospective studies of rituximab-containing chemotherapies are warranted.

365 PRIMARY TONSIL NON-HODGKIN'S LYMPHOMA, CLINICAL CHARACTERISTICS, PROGNOSIS AND SURVIVAL ANALYSIS

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Objectives: This study aimed to analysis the clinical characteristics, prognostic factors and treatment outcome of Chinese patients with primary non-Hodgkin's lymphoma (NHL) of tonsil.

Methods: From May 1990 to March 2007, 106 patients with previously untreated NHL of tonsil were retrospectively reviewed. The median age was 49 years. In theall 106 patients, 68.9% diagnosed of diffuse large-B-cell lymphoma (DLBCL), 11.3% of peripheral-T-cell lymphoma (PTCL) and 7.5% of indolent B-cell lymphoma. Ninety-eight (92.5%) patients presented with stage I and II disease. Majority of patients (69.8%) received combined chemoradiotherapy and 17.9% treated by radiotherapy alone as initial treatment. The predominant chemotherapy regimens were CHOP and BACOP, and radiotherapy dose range between 40-50Gy.

Results: After a median follow-up of 51 months, the estimate 5-year overall survival (OS) and disease free survival (DFS) were 82% and 68%, respectively. Significant prognostic factors included: advanced disease and locally extra-nodal involvement. Other prognostic factors, such as age older than 60 years, B symptoms, bulky disease, T cell lymphoma and treatment modalities as chemoradiotherapy or radiotherapy alone did not show significant results on outcome.

Conclusions: Survival for the patients with primary tonsil NHL is optimal as most of the patients have stage I or II diseases. Diffuse large-B-cell lymphoma is the most common pathological subtype. Multivariate analysis by Cox regression shows that advanced stage, primary refractory disease and locally extra-nodal infiltration are independent prognostic factors.

Keywords: tonsil neoplasms; Non-Hodgkin's lymphoma; chemotherapy; radiotherapy

366 DIFFUSE LARGE B-CELL LYMPHOMAS OF THE WALDEYER'S RING: A CLINICO-PATHOLOGICAL STUDY OF 209 PATIENTS FROM THE GROUPE D'ETUDE DES LYMPHOMES DE L'ADULTE (GELA)

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DLBCLs are markedly heterogeneous, and their biological features may vary according to the primary site of disease. The WR is the second most common site of extranodal involvement by DLBCL.

We analyzed 209 adult patients with *de novo* DLBCL presenting in the WR consecutively included in the GELA trials (1993-2004) (M/F: 1,8; mean age 59 yrs; 81% stages I-II) and treated with anthracyclin-based polychemotherapy. Morphology and immunophenotype were analyzed and correlated to the clinical features. FISH assays with split-signal DNA probes were performed on a subset of cases. Survival and outcome were compared to a matched cohort primary nodal DLBCL patients.

By morphology, 55% of WR DLBCLs were centroblastic, 39% centroblastic-polymorphous, 3% immunoblastic, and 3% unclassifiable. Among large biopsy specimens (n=79), 53% had a prominent or minor nodular pattern and 47% were purely diffuse. The prevalence of antigen expression was: bcl2: 105/189 (60%); CD10:

75/178 (42%); bcl6: 40/76 (53%); mum-1:40/109 (37%). The immunophenotype of 136 cases was GC-like in 60% and non-GC-like in 40%. In multivariate analysis, GC-like cases correlated with better OS (p=0.014). Rearrangement of *BCL-2*, *BCL6* and *c-MYC* loci were found by FISH in 3/42, 9/35 and 3/41 cases. For 144 paired WR/nodal cases, the CR rate was significantly better for WR patients (p=0.01) but the 5-y OS and EFS rates (79,7% and 70,9% in WR patients, and 76,7% and 66,7% in nodal patients) did not significantly differ. For 109 paired patients with no adverse prognostic factor of the aa IPI, primary WR localization was associated with a higher 5-y EFS (78,5% *vs.* 71,2%; p=0,029) and 0S (84,7% *vs.* 79,8%; p=0,047) rates.

In conclusion, WR DLBCLs frequently have a partially follicular pattern of growth, and a GC-like phenotype. In DLBCL patients with an aa IPI = 0, the WR localization appears to confer a better outcome than primary nodal involvement.

367 RITUXIMAB MONOTHERAPY IS THE TREATMENT OF CHOICE OF SPLENIC MARGINAL ZONE LYMPHOMA (SMZL)

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Introduction: There is no standard therapy for SMZL. Splenectomy has been considered as the first line treatment although it may carry significant complications. We present our results on the efficacy of Rituximab as a first line treatment in SMZL patients (pts).

Patients and methods: We analysed 24 pts with SMZL diagnosed in our Dpt between 2003 and 2007. All pts received Rituximab at a dose of 375mg/m^2/week for 6 consecutive weeks at a median time of 1,5 mo after diagnosis. Maintenance therapy (MTh) was given as one dose of 375mg/m^2 Rituximab every 2 mos for one year. Pts' median age was 57 years (range 48-78). At diagnosis all pts had splenomegaly and bone marrow infiltration. Response criteria were defined as follows: CR: complete clinical, morphologic and immunophenotypic remission, unconfirmed CR: clinical and laboratory CR without bone marrow evaluation, PR: 50% improvement of clinical and laboratory features.

Results: Overall response was 100%. All pts had complete resolution of splenomegaly at a median time of 5 weeks (median 2-15) after treatment initiation along with restoration to normal of their blood counts at a median time of 4 weeks (1-44). 17 pts (71%) achieved a CR, 4 an unconfirmed CR (17%), and 3 (12%) a PR. Among the CR's 5 pts had also a molecular remission. 20 pts underwent MTh, while 4 did not. 12/20 pts have already completed MTh. 10/12 pts who completed MTh sustained their response and 2 pts achieved an improvement of response. 2 relapses were recorded at a median time of 21,5 mos. Median follow up time for the entire series is 29 mos (range 6-91). No deaths were recorded.

Conclusions: The present study demonstrates that Rituximab is a highly effective treatment for SMZL. It confers better response rates in relation to other treatment modalities used so far. MTh also appears to be important for consolidation or even further improvement of response.

368 ACTIVITY OF BORTEZOMIB IN MALT LYMPHOMAS: A IELSG PHASE II STUDY

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The International Extranodal Lymphoma Study Group (IELSG) is coordinating a phase II trial aimed to assess the antitumor activity and safety of bortezomib in patients (pts) with relapsed or refractory extranodal marginal zone B-cell lymphoma of MALT-type. Bortezomib 1.3 mg/m^2 is administered on days 1, 4, 8, and 11 of a 21-day cycle, for up to 6 cycles. Response and progression are determined by International Workshop Criteria. As of January 2008, 25 pts have been enrolled in the study: among the 21 pts in whom the data are available, 12 (57%) patients were male, median age was 63 years (range, 38–81). At time of enrolment, the Ann Arbor stages distribution was the following: stage I=5 pts (24%), stage II=5 pts (24%), stage IV=11 (52%). In 11 pts primary gastric localization was present, in 5 cases primary skin, in 2 cases primary subcutaneous, moreover a primary lung, orbit, muscle localization was reported in 1 pt each. All patients had ECOG PS=0; in 3 cases (14%) elevated serum LDH was reported. More than 1 site of extranodal localization was present in 5 pts (24%). Median number of prior therapies was 2 (range, 1–3). Median follow-up was 17 months. Eleven pts were assessed for response at the end of treatment plan: 3 pts had a CR (27%); 4 a PR (37%) and 3 SD (27%) and 1 a PD (9%). Four additional pts, with ongoing therapies, have been evaluated after the first two courses of therapy: one pt achieved a CR, 1 pt a PR, 1 pt a SD and in 1 a PD was observed. Significant duration of response was observed among the 4 pts in CR, ranging from 18 to 22 months and in most cases still ongoing. The safety profile of bortezomib is similar to that observed in multiple myeloma and other subtypes of non-Hodgkin lymphoma. The most relevant grade 3 or higher adverse events were peripheral neuropathy and fatigue. Three deaths, non-related to treatment, were observed during the early follow up. These preliminary results suggest that bortezomib is active and safe in relapsed or refractory MALT lymphomas and encourage us to complete the studies accrual.

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