# DLBCL

## 440 FCGAMMA RECEPTOR IIIA POLYMORPHISM AND GENE EXPRESSION PROFILE AS POSSIBLE NEW PROGNOSTICAL FACTORS OF DIFFUSE LARGE B-CELL LYMPHOMA

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Treatment responses and survival rates are different among patients with diffuse large B-cell lymphoma (DLBCL) which might be related to some novel prognostic markers.

Our aim was to examine if treatment and survival results are influenced by Fcgamma receptor IIIa polymorphism (FCGR3A) and gene expression profile (GEP).

Between 2007 and 2009 thirty-four newly diagnosed DLBCL patients (19 females, 15 males, mean age: 51.7 years) were treated with R-CHOP-14 protocol in our hospital. Among them, FCGR3A polymorphism was examined at the 158. amino acid position with polymerase chain reaction, while GEP including bcl-2, bcl-6, CD10, CD30 and MUM-1 markers was investigated using fluorescence in situ hybridization (FISH).

Considering FCGR3A polymorphism, the distribution of genotypes was the following: 7 (20%) VV, 5 (15%) FF and 22 (65%) VF. Treatment responses were not significantly different in the three genotype groups. Event-free survival (EFS) was less favourable in patients bearing the F allele, however, the difference was not significant (p=0.163) and overall survival (OS) rates were almost the same. Examining the gene expression profiles, ten cases (29%) were found to be of germinal center (GC) origin, while twenty-four (71%) patients had lymphoma of non-GC origin. There was no difference in their treatment responses, however OS and EFS rates were more favorable in the GC group (p=0.162).

Our results highlight that the prognostic values of both FCGR3A and GEP are still controversial.

## 441 PERIPHERAL BLOOD MONOCYTOSIS IS AN INDEPENDENT PROGNOSTIC FACTOR FOR SURVIVAL IN DIFFUSE LARGE B CELL LYMPHOMA (DLBCL)

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**Background:** Peripheral blood monocytosis (PBM) has been reported in some cases of malignant lymphoma but its prevalence in DLBCL is not known. Recent in vitro studies have shown that monocytes can promote the survival of lymphoma cells and gene expression profiling done on lymph nodes have illustrated that monocytes/ monocyte like dendritic cells infiltrating the tumor environment, play a major role in enhancing the survival of lymphoma cells, displaying immune suppressive function. Recently, we encountered PBM in some patients with DLBCL who had a rapidly progressive fatal course, This observation and the recent emerging data regarding the stromal role of immune cells, led us to undertake a retrospective study to determine prevalence of PBM and its possible prognostic significance in patients with DLBCL.

**Patients and Methods:** Clinical and laboratory data from the medical records of 91 patients with DLBCL treated in our institute during 1996-2010, were evaluated for the presence of absolute monocytosis, (> 1000 cells/ mm3) before treatment and possible correlations with other prognostic factors: B symptoms, age, stage, gender, extra nodal involvement, serum LDH and CRP, bone marrow (BM) involvement, and the IPI score. A Cox proportional hazards regression model was used to determine the significance of the prognostic factors in a multivariate analysis.

**Results:** Median follow up was 30 months (1-332 months) and PBM was found in 18.3% of patients at presentation. In the univariant analysis, PBM, IPI score, stage, LDH, and BM involvement were all associated with a worse prognosis. In the multivariate analysis (Cox model), only PBM, BM involvement and IPI were found to be independent prognostic factors for overall survival (os).

| | Hazard Ratio | 95% HR | | Pr > ChiSq |
|---|---|---|---|---|
| IPI | 5.317 | 2.276 | 12.424 | 0.0001 |
| MONO >1000 | 3.127 | 1.154 | 8.475 | 0.0250 |
| BM.involved | 3.809 | 1.487 | 9.757 | 0.0053 |

**Conclusions:** This study indicates that PBM is an independent prognostic value associated with poor prognosis and os in patients with DLCL. This easily applied routine laboratory test can be readily utilized and potentially significant results can be quickly obtained. We recommend that it be considered as a simple additional indicator of poor outcome in DLBCL. These findings provide further support for the importance of monocytes and their functional role in the immune response in DLBCL. Studies on their involvement in the biology of DLBCL are now in progress in our laboratory

## 442 WITHDRAWN

## 443 LACTATE DEHYDROGENASE LEVELS DO NOT PREDICT RELAPSE IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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**Introduction:** Lactate dehydrogenase (LDH) is of prognostic importance at diagnosis & at relapse in patients (pts) with DLBCL. It is also frequently monitored during follow-up (FU) to detect pre-clinical relapse, however the evidence for this role is limited. We performed a retrospective study investigating the utility of LDH in predicting relapse, in pts with DLBCL who had achieved a CR with 1st-line chemotherapy (chemo).

**Methods:** Pts with DLBCL treated between 2000-09 & who achieved a CR were included. Baseline characteristics, treatment received & current status were logged. All LDHs measured from 2mo after completion of chemo to last FU were recorded. If LDH was raised at any point, any additional investigations performed were noted.

Pts were grouped into 4 categories: LDH normal/no relapse n=35 (never had a raised LDH & in CR); LDH raised/no relapse n=54 (had at least one raised LDH- above the upper limit of normal (ULN) but remained in CR); LDH normal/relapse n=4 (relapsed but had normal LDH levels for the 6mo preceding relapse); LDH raised/relapse n=9 (LDH raised at least once in the 6mo prior to relapse). The predictive values were calculated with 95% confidence intervals (CI) using Fisher's exact test. The analysis was repeated, using a cut-off LDH of >25% ULN; & thirdly to see whether at least 2 raised LDHs (more than 3 mo apart) rather than just a single raised LDH was more predictive.

**Results:** 102 pts (median age 66) had a median FU of 24 mo (range 2-76). 64 pts had a raised LDH at diagnosis. 13 pts relapsed (median time to relapse 6 months (range 2-33), LDH was raised in 9 pts and 11/13 had symptoms/signs of relapse at the time. The median level of LDH at relapse was 668 IU/L, compared to median LDH at last FU in the pts who remain in CR of 466 IU/L (p=0.0002). The positive predictive value (PPV) of a raised LDH during FU was only 14% (CI 6.7-25), & the negative predictive value (NPV) was 90% (CI 76-97). The sensitivity & specificity of a raised LDH was 69% (CI 39-91) & 39% (CI 29-50) respectively. When using >25% ULN LDH as the cut-off, the PPV was 13% (CI 1.6-38) with NPV of 87% (CI 78-93). Repeating the analysis & including only pts who had at least 2 raised LDHs in the group ''raised LDH'' revealed a PPV 11% (CI 3.1-26) & a NPV 86% (CI 76-94).

**Conclusions:** Although the *median* LDH is significantly higher in pts who have relapsed compared to those who remain in CR, the PPV of a raised LDH is very low & thus in the clinic setting, the LDH value is not useful at predicting relapse & can lead to unnecessary investigations & worry for the pt. Furthermore, in our group, the majority of pts who relapsed had clinical features as well as a raised LDH.

## 444 MINIMAL RESIDUAL DISEASE MONITORING IN PATIENTS WITH PHILADELPHIA-CHROMOSOME POSITIVE (PH+) ACUTE LYMPHOBLASTIC LEUKEMIA (ALL) TREATED WITH THE COMBINATION OF HYPERCVAD AND A TYROSINE KINASE INHIBITOR

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**Background:** The outcome of patients with Philadelphia-chromosme-positive (Ph+) acute lymphoblastic leukemia (ALL) has improved significantly with the addition of tyrosine kinase inhibitors imatinib and dasatinib to combination chemotherapy regimens. We examined the potential role of detection of minimal residual disease (MRD) measured by multiparameter flow cytometry (MFC) or reverse transcription quantitative polymerase chain reaction (RQ-PCR), at specific time points during therapy, in predicting relapse.

**Materials and Methods:** From April 2001 to September 2006, 54 pts with newly diagnosed Ph+ ALL were treated with the combination of hyperCVAD and imatinib; from October 2006 to July 2009, 42 pts were treated with the hyperCVAD and dasatinib regimen. The median ages for the two groups were 50 and 51 years [ranges, (27 - 84) and (21 - 78)]. Fifty one (94%) and 40 (95%) achieved complete remission (CR) on the two regimen and were followed by serial bone marrow assessments for MRD. MFC was performed using 4 or 6 color combinations of antibodies to lymphoblast and myeloid

antigens with a sensitivity of 0.01%. RQ-PCR for *BCR-ABL* was performed using TaqMan primer/probes for the e1a2, e13a2 (b2a2), and e14a2 (b3a2) *BCR-ABL* transcripts in a single tube with normalization to total *ABL* transcripts. We determined the predictive value of a positive MFC test, or a *BCR-ABL/ABL* ratio > 0.1% (MMR) at CR and at the end of consolidation (EOC; approximately 6 to 12 months after initiation of therapy) in predicting relapse.

**Results:** Among the 96 patients treated on the two regimens, 91 (95%) achieved CR. 69 patients were de novo without any prior treatment for ALL, Samples for MFC were available at CR, and at EOC in 50 and 26 patients; available results for *BCR-ABL* were also available at those time-points in 56 and 23 patients. 5 of 18 patients with a positive MFC at CR relapsed compared with 8 of 32 with a negative test (p=0.83). 4 of 4 with a positive MFC at EOC relapsed compared with 4 of 22 with a negative test (p=.001). Among patients with available BCR-ABL results at CR, 7 of 25 patients with a MMR (*BCR-ABL/ABL*<0.1%) at CR relapsed compared with 10 of 31 with less than MMR (*BCR-ABL*≥ 0.1%) (p=0.73). 3 of 6 patients with MMR at EOC relapsed compared with 4 of 17 with less than MMR at EOC (p=0.13).

**Conclusions:** A positive MRD by MFC at EOC is associated with a higher likelihood of relapse but achieving MMR at EOC does not protect against relapse. This data may help in devising risk-adapted therapy in patients with Ph+ ALL.

## 445 SAFETY, EFFICACY AND PHARMACOECONOMIC ANALYSIS (PA) OF RAPID INFUSION (RI) OF RITUXIMAB WITHOUT INFUSION PUMP (IP) IN NON-HODGKIN LYMPHOMAS (NHL): EXPERIENCE OF A BRAZILIAN PUBLIC HOSPITAL

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**Introduction:** Rituximab, a monoclonal chimeric anti-CD20, has been widely used in the management of NHL even in patients in the National Health System (NHS). The increase in the use of this monoclonal antibody (MA) in the treatment of NHL with a long infusion time (standard infusion-SI) is resulting in overload of chemotherapy services primarily concentrated in the NHS where most patients undergo treatment. The RI of rituximab after the second dose for 90 minutes with IP seems to solve this problem. Objective: evaluate the characteristics of patients with NHL who received RI of rituximab without IP at Santa Marcelina Hospital as well as efficacy, safety and PA of the RI of rituximab.

**Material and Methods:** We retrospectively evaluated 51 patients with NHL who received RI of rituximab between April 2009 and January 2011. The diagnosis of NHL was based on histopathological analysis and immunohistochemistry of biopsy. We used Ann Arbor staging and International Prognostic Index (IPI) for prognosis and the NCIW group criteria to assess response. The criterion of NCI during reactions infusions of MA to assess toxicity was used. The Kaplan-Meier method to evaluate overall survival (OS) and progression-free survival (PFS) was also used. The EXCEL program projected the number of additional type R-CHOP chemotherapy that would be performed by reducing the infusion time for the introduction of RI and the economy of this protocol by subtracting the values passed on by the NHS versus total expenditure (drugs, supplies, fees).

**Results:** 30 patients were male and 21 female, average age of 59 (20-82). Of the 51 cases of NHL, 34 were aggressive and 17 indolent with Ann Arbor stage I, II (14) and III, IV (37), low IPI in 11 patients, intermediate in 37 and 3 high IPI. 192 RI of rituximab were performed with an average of 3.8 per patient and a mean follow-up of 38 months. We observed only 2 cases of mild reactions and 4 deaths where 3 of them were related to the disease. Of the 51 patients evaluated, 86% had CR corresponding OS of 88% and PFS of 80%. PA found that 16 cases would be treated more in this new period using RI of rituximab with an economy of US $55,099.67 to the transfers of NHS.

**Conclusion:** The RI of rituximab without IP was safe, with high rates of CR, OS, PFS and pharmacoeconomic advantage compared to SI. Moreover, for the first time ever in literature it was found that a RI of rituximab has a similar efficacy to SI. These results certify the use of RI of rituximab as standard protocol in patients with NHL particularly those treated by the NHS.

## 446 COMPREHENSIVE SYMPTOM PROFILE IN PATIENTS WITH MALIGNANT LYMPHOMAS: PRACTICABILITY AND SENSITIVITY OF THE NEW SYMPTOM ASSESSMENT TOOL CSP-LYM

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Symptom profile and severity is one of the important treatment outcomes in patients with malignant lymphomas. Comprehensive symptom assessment and monitoring before and during treatment as well as at follow-up is worthwhile. Recently a new tool, Comprehensive Symptom Profile in Lymphoma Patients (CSP-Lym), has been developed to assess symptoms specific for patients with malignant lymphomas. We aimed to test practicability and sensitivity of CSP-Lym. A total of 106 patients with different types of malignant lymphomas (Stage – II-IV) were included in the study: non-Hodgkin's lymphoma–45; Hodgkin's lymphoma – 61. Mean age was 34.8 years old; male/female distribution–43/62. Thirty two patients underwent conventional chemotherapy (CT), and 74 patients–high-dose chemotherapy with autologous haematopoietic stem cell transplantation (HDCT+AHSCT). The patients filled out the CSP-Lym before treatment and at different time-points thereafter. CSP-Lym is developed to assess the severity of 41 symptoms specific for patients with malignant lymphomas. Practicability of the CSP-Lym was shown: patients needed 7-10 min to answer it; the proportion of missing values was less than 1% for all questions; the questionnaire found high acceptance reflected by no refusals. Usefulness of the CSP-Lym to distinguish patients in terms of severity and number of symptoms experienced was demonstrated. Changes in symptom profile and severity during and after CT were used by the hematologists for the decision-making. Information about symptom profile and severity at long-term follow-up after HDCT+AHSCT was an indicator of the degree of recovery. In a year after HDCT+AHSCT reduction in the majority of symptoms (75%) was observed: the severity of 7 symptoms decreased significantly ($p < 0.05$). Decrease in the number of patients experiencing moderate-to-severe symptoms after HDCT+AHSCT was shown. CSP-Lym is a sensitive and practical tool to assess symptom profile and severity in patients with malignant lymphomas. Comprehensive symptom monitoring is recommended to clearly determine treatment outcomes in patients with malignant lymphomas.

## 447 UTILIZATION RATE AND REAL-WORLD OUTCOMES OF USING INNOVATIVE TREATMENT IN B-CELL NON-HODGKIN'S LYMPHOMA IN THE DEVELOPING WORLD: AN EXPERIENCE FROM THAILAND

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**Background:** The addition of rituximab to chemotherapy (R-chemotherapy) significantly improves outcomes in patients with B-cell Non-Hodgkin's Lymphoma (B-cell NHL) as shown in randomized clinical trials and population-based studies. R-chemotherapy has been used as the standard therapy for diffuse large B-cell lymphoma (DLBCL) and follicular lymphoma in the western world. In Thailand, limited resources have played an important role in determining access to innovative treatments such as rituximab. At Siriraj Hospital, one of the principal medical schools, the real-world use of R-chemotherapy and associated outcomes had never been explored.

**Method:** Medical records of patients who were newly diagnosed with B-cell NHL during 2000-2006 were retrospectively reviewed. Results on demographics, baseline characteristics, treatments and outcomes were captured. Statistical analyses were performed based on the follow-up through June 2010.

**Results:** Of 848 NHL patients, a total of 497 patients were diagnosed as B-cell NHL. The majority of B-cell NHL patients (75.7%) was identified as having DLBCL while 9.9% was identified as having follicular lymphoma. Three-fourth of patients received chemotherapy alone while one-fourth received R-chemotherapy. The use of chemotherapy had decreased from 98.3% in 2000 to 68.8% in 2006 while the use of R-chemotherapy had increased from 1.7% in 2000 to 31.3% in 2006. Since the launch of rituximab in 1999, R-chemotherapy had been taken-up within 4 years, reaching the saturated utilization rate at 31.3% in 2003. The utilization rate was found to be constant during 2003 to 2006 with the maximum rate of 32.7%. With a median follow-up of 4.9 years, median event-free survival (EFS) and median overall survival (OS) in the chemotherapy group was 12.4 months and had not yet been reached, respectively. While median EFS and median OS in the R-Chemotherapy group was 48.2 months and had not yet been reached, respectively (EFS: $p = 0.012$ and OS: $p = 0.123$) The addition of rituximab to chemotherapy was a favored independent factor for EFS with hazard ratio of 0.394 ($p = 0.045$), whereas having an elevated serum lactate dehydrogenase had deleterious effect on EFS with hazard ratios of 2.310 ($p = 0.038$).

**Conclusions:** The results of this study have brought further support for the use of R-chemotherapy in these patients. Public health policy and resource allocations are in need to reduce barriers to innovative treatment for B-cell NHL patients in Thailand.

## 448 DIFFUSE LARGE B-CELL LYMPHOMA: GERMINAL CENTER VS NON GERMINAL CENTER - TREATMENT RESPONSE ON IMMUNOCHEMOTHERAPY. SERBIAN LYMPHOMA STUDY GROUP

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**Background:** Recent studies divided diffuse large B-cell lymphoma (DLBCL) into germinal center B-cell like (GCB) and non germinal center B-cell like (non-GCB) subgroups, which showed prognostic significance. The addition of rituximab to chemotherapy brought survival benefit in both subgroups.

**Patients and Methods:** We studied 99 patients with de novo DLBCL treated with R-CHOP 21 immunochemotherapy. The patients were obtained from Serbian National Lymphoma Register (the enrolement started from April 2008). The division to GCB and non-GCB subgroups was made based on immunohystochemical findings by using the Hans method. The baseline characteristics that were correlated with immunophenotype were age, sex, IPI score, Ann Arbor Clinical Stage, ECOG performance status, presence of B symptoms, bulky disease, extranodal disease, spleen enlargement, number of involved lymph node areas, bone marrow involvement, ESR, LDH level, β2-microglobulin, CRP, Hgb level, WBC count, platelets count, total serum proteins and albumin. Also, bcl-2 expression and different levels of Ki-67 expression were correlated.

**Results:** Thirty patients (30.3%) expressed GCB phenotype. In our analysis, there was no difference regarding the complete remission (CR) rate. The only difference in baseline characteristics between the GCB and non GCB patients was recorded in presence of leucocytosis, the non-GCB patients had significantly higher WBC count (31.9% vs 10%, $p<0.05$). In both subgroups, the WBC count, didn't have an impact on CR rate.

**Conclusions:** According to our experience, the presentation of DLBCL doesn't depend on immunopenotypic subtype. The observed high percentage of elevated WBC and its prognostic significance for survival in non-GCB patients should be examined in larger series of patients.

## 449 WITHDRAWN

## 450 PHARMACOKINETICS OF RITUXIMAB IN COMBINATION WITH CHOP-14 AND CHOP-21 CHEMOTHERAPY IN DLBCL

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**Background:** Because of the scarcity of data in diffuse large B-cell lymphoma (DLBCL), rituximab pharmacokinetics in combination with CHOP-14 and CHOP-21 was studied in patients with DLBCL.

**Material:** Serum rituximab levels were investigated in 36 patients who were treated at different centers participating in the prospective multicenter UNFOLDER trial of the DSHNHL (NCT00278408), where in a randomized fashion an immunochemotherapy with 6 cycles of rituximab in combination with 6 cycles of chemotherapy with CHOP at 21-day intervals or 14-day intervals were compared, both with or without consolidating radiotherapy to bulky disease (≥7.5 cm) and/or extranodal involvement in patients with proven aggressive CD 20 positive B-Cell Lymphoma aged 18 to 60 years with age-adjusted IPI=1 (all) or IPI=0 with bulky (≥7.5 cm). Ten minutes before and ten minutes after the rituximab infusion in each immunochemotherapy cycle, 10 mL of blood were drawn from each subject to obtain rituximab trough and peak (data not shown) levels. Additional samples were taken 1 month, 2 months, 3 months and 6 months after the last rituximab infusion. Rituximab serum levels were determined by Xendo Laboratories, Groningen, NL by an enzyme-linked immunoabsorbent assay.

**Results:** Eighteen patients were included in pharmacokinetic analysis of each arm of the trial. 2 week- application of rituximab showed a more rapid increase of serum rituximab levels (day 70 vs. 135) and higher maximal levels (125 μg/mL vs. 95 μg/mL) compared to the standard 3-week protocol (see Table 1). Surprisingly, despite the fact that the last application of rituximab in the 2-week regimen was given in week 10 compared to week 15 in the 3-week regimen, the rituximab serum levels in the 2-week regimen persisted as long as those in the 3-week regimen.

**Conclusion:** 2 week application of rituximab is associated with a more rapid increase of serum rituximab levels and higher maximal levels, while rituximab serum levels are maintained as long as in the 3-week regimen. This results in a greater area under the curve for the 2-week regimen compared to the 3-week regimen. Longer follow-up is needed to see whether the greater area under the curve is associated with better results for R-CHOP-14 over R-CHOP-21 in this randomized trial. The results of this study serve as a basis for future protocols aiming at optimizing the use of rituximab in DLBCL.

## 451 RADIOIMMUNOTHERAPY FOR CONSOLIDATION AND RELAPSE TREATMENT OF AGGRESSIVE B-CELL NON HODGKINS LYMPHOMA: AN UPDATED ANALYSIS OF THE INTERNATIONAL RIT-NETWORK

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Radioimmunotherapy (RIT) for lymphoma with labelled anti-CD 20 antibodies has shown high response rates and durable remissions in extensively pretreated patients (pts). In aggressive lymphoma, data are sparse, and studies with RIT as consolidation and relapse are ongoing.

Data of pts with DLBCL registered in the international RIT-Network (RIT-NT) were analyzed with regard to Indication, line of therapy and outcome. The RIT-NT is a web-based registry that collects observational data from RIT-treated patients with malignant lymphoma from across the world.

232 patients with DLBCL were evaluated in the following analysis. 232 pts with DLBCL are registered, 17 pts had to be excluded. Histologic subtypes: 190 diffuse large B-Cell, 15 primary mediastinal, 9 large cell anaplastic, 1 intravascular. Median age 62 years (range 17-88), 27% > 70 years old. Stage : stage I 16pts , II 54 pts, III 60 pts, IV 68 pts; 6 extranodal involvement, for 11 pt. stage is not documented. 187 pts had 1-3 previous chemotherapies (Ctx), 21 pts 4-6 previous Ctx, 1 pts had seven previous Ctx, for 6 pts previous Ctx is not documented. 15 pts had previous RIT and 24 pts a stem cell transplantation prior to RIT. 6 pts had bone marrow infiltration prior to RIT, 3 with infiltration of more than 25%. 87 pts had RIT as first line (8 pts as part of the conditioning, 68 pts consolidation, 1 primary therapy, 10 other), and 84 pts received RIT in relapse (2d to 8 th. line therapy) (2 pts as part of the conditioning, 31 pts consolidation, 26 recurrence, 19 therapy refractory, 6 other). Grade IV° Haematotoxicity occured for neutrophils and platelet, grade III° for haemoglobin after RIT. Median time to recovery of blood count was 81 days (range 0-600 days). Overall response rate was 60 %; CR 50%; PR 10%, SD 1%, PD 26%, N.D. 15%. CR rate for first line pts was 75 %, for relapse 37%. Mean overall survival (OS) in first line therapy was 788 days and 446 days for pts treated in relapse or refractory disease.

Most pts with DLBCL receive RIT as consolidation after first line therapy with excellent CR rates and OS. Also for pts in relapse RIT is a safe and feasible treatment leading to satisfactory response rates with a low toxicity. Especially in elderly pts not fit for very aggressive chemotherapy and/or stem cell transplantation, RIT should continue to be explored in prospective clinical trials.

## 452 PHASE 2 STUDIES OF IMMUNOCHEMOTHERAPY ± BORTEZOMIB (VC) IN NEWLY DIAGNOSED NON-GERMINAL CENTER B-CELL-LIKE (GCB) DLBCL: RAPID PROSPECTIVE IDENTIFICATION OF NON-GCB PATIENTS (PTS)

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**Introduction:** LYM2034 (non-US) and PYRAMID (US) are prospectively enrolling pts with non-GCB DLBCL, which has inferior outcomes vs GCB DLBCL following (R-)CHOP. Prior studies suggest Vc has benefit specifically in NF-κB-dependent non-GCB DLBCL, consistent with Vc-mediated inhibition of the NF-κB pathway. We report operational aspects of real-time pathology assessments in both studies.

**Material and Methods:** Pts aged ≥18 yrs with ECOG PS 0–2 are eligible. Non-GCB tumor subtyping is done at a US central laboratory via the Hans IHC assay (CD10-, and BCL6-, or BCL6+ and MUM1+). Non-GCB pts are randomized to six 3-week cycles of R-CHOP, vs Vc 1.3 mg/m$^2$ (d 1, 4, 8, 11) + R-CAP (R-CHOP minus vincristine; LYM2034) or Vc 1.3 mg/m$^2$ (d 1, 4) + R-CHOP (PYRAMID).

**Results:** In LYM2034, 167 pts have been screened, 75 identified as non-GCB DLBCL, and 62 randomized. In PYRAMID 100 pts have been screened, 39 identified as non-GCB DLBCL, and 34 randomized. Mean time from receipt of sample to subtype reporting is 5.6 days in LYM2034 and 1.2 business days in PYRAMID; mean time for return of pathology block to clinical site is 2-3 weeks and 4.4 days, respectively. Results using the Hans algorithm are being compared with those using the Choi and Tally algorithms; initial analyses show high concordance.

**Conclusions:** LYM2034 and PYRAMID demonstrate that prospective enrichment of non-GCB DLBCL pts is feasible with rapid subtype identification. These studies continue to enroll pts.

## 453 LIPOSOMAL CYTARABINE (DEPOCYTE) IN PROPHYLAXIS AND TREATMENT OF CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT OF AGGRESSIVE, HIGH RISK LYMPHOMA

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**Background:** DepoCyte is a sustained-release formulation of cytarabine, characterised by biphasic elimination profile with a terminal phase half-life of 100 to 263 hours over 50 times longer than free cytarabine designed specifically for intrathecal administration.

**Materials And Methods:** Eighty five patients with aggressive high risk NHL received Depocyte either as prophylaxis (N=60) or treatment (N=25) of central nervous system (CNS) involvement. In patients receiving prophylaxias, high risk was defined as presence at least 2 of the following: elevated LDH (n=53, 88%), involvement of 2 or more extranodal sites (n=20, 33%), IPI 3-5 (n=36, 61%) and specific lymphoma localizations (testis, vertebral column, orbits, sinuses, bulky mediastinal tumor; n=36, 60%). None of the patients had neurological symptoms at diagnosis, nor any abnormalities in imaging studies or cerebrospinal fluid analysis (average cellularity 2.5/$mm^3$, range 0-9). In the treatment subgroup, disease was confirmed by CNS fluid cytology in 18/25 (72%) patients (average cytosis 128, range 19-650) and/or imaging studies (20/25, 80%) at diagnosis (n=15, 60%) or at relapse (n=10, 40%).

**Results:** In prophylaxis Depocyte 3.4 doses (2-6) were administered at a time of chemotherapy cycles, eliminating necessity for additional hospital admissions every 2 (n=47) or 3(n=13) weeks. At medium observation time of 14 (1 -32) months 54/60 (90%) patients were alive, without CNS relapse. Only 2 (3.3%) cases relapsed (a systemic/CNS relapse in lymphoblastic lymphoma and isolated CNS relapse in DLBCL patient after 8 and 18 months respectively). Treatment of CNS disease consisted of 4.6 doses (1-8) with concomitant chemotherapy in 57 % and subsequent radiotherapy in 52% of cases. The median OS and EFS were 33 months and 20 months respectively.

**Conclusions:** In prophylaxis Depocyte proved to be an efficient, convenient and well tolerated drug reducing number of relapses in a high risk aggressive NHL to 3.3%. Used in a treatment setting it prolonged response duration and improved quality of life.

## 454 HEPATIC TOXICITY IN PATIENTS WITH NON HODGKIN'S LYMPHOMA (NHL) INFECTED WITH HEPATITIS C UNDERGOING CHEMOTHERAPY WITH RITUXIMAB

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It's shown that virus hepatitis C (HCV) is one of etiopathogenic factors of NHL. It's shown that level of various markers of HCV at patients from NHL can be taped at 30 % of patients (pts). In literature well-known role of hepatitis B at carrying out immunochemistry (ICH). The hepatitis C at ICT is studied little.

In our research we studied function of liver at pts with NHL at carrying out ICT with markers of HCV and without them. 64 pts with NHL have been included in research with markers HCV infection and 196 without it by which it has been spent ICT. Pts with HCV infection was 21 pts with indolent lymphoma (IL), 41 diffuse large B cell lymphoma (DLBCL) and 2 with chronic lymphocytic leukemia (CLL). The age median has made 47 years. III-IV stages of disease were at 52 patients, 11 II stage and 1 IE. Normal level ALT and AST prior to the beginning of treatment was at 16 patients. At beginning of treatment was from 0 to $4.2x10^6$/ml. The median serum level HCV RNA was $2.3x10^5$/ml. Pts without HCV infection there were 47 patients about IL, 94 DLBCL and 55 with CLL. The age median was 54. III-IY st was at 69 pts, I-II at 72 pts. Normal level ALT and AST was at 167 pts. All pts were treated by R-CHOP or R-FC.

Serum level HCVRNA has increased at 39 of 64 pts. At all 39 pts before therapy had positive serum level HCV RNA. Level of HCV RNA was from $3ч10^5$ to $8.8x10^7$/ml a median has made $4.2x10^6$/ml. 37 from 64 pts simultaneously with increased serum level HCV RNA increased level ALT and AST. Level ALT was from 2 to 50 norms, median- 7.5 norms. Level AST increased at 43 pts from 2 to 10 norms, median of 4.5 norms. The reason of stop treatment at 19 pts was hepatic toxicity. Complete remission (CR) in Pts with HCV infection has been reached at 14 about IL and 12 DLBCL. Median follow up was 12 months.

Among 196 pts without HCV infection increased level ALT and AST only at 15 pts. Median was 2.3 norms. HCV RNA was not defined at all this 15 pts. The treatment has not been stopped at any pts thanks to hepatic toxicity. CR has been reached at 28 about IL and 56 with DLBCL. Median follow up was 28 months.

Significant proportion of patients with HCV + NHL develop liver toxicity often leading to interruption of treatment. This could be limit to the application of immunochemotherapy programs. HCV + lymphomas represent a distinct clinical subset of NHL that deserves specific clinical approach to limit liver toxicity and survival.

## 455 A STUDY COMPARING METHODS OF ASSESSING CARDIAC DAMAGE IN TREATED LYMPHOMA PATIENTS

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**Background:** Heart disease is the most common non-malignant cause of morbidity and mortality among lymphoma survivors. Anthracycline chemotherapy can contribute to heart muscle damage while radiation may affect pericardium, myocardium or coronary vasculature. Combined modality therapy is thus especially likely to confer late cardiac damage. Attempts to screen for heart disease have focused on use of echocardiograms but it appears this is not sensitive in detecting early signs of damage. Serum BNP (brain natriuretic protein) is used increasingly in cardiology to screen populations and has been shown to be a reliable predictor for damage. The gold standard for assessing function is cardiac magnetic resonance. We designed this study to determine whether serum BNP might suffice as an early marker for damage, comparing against cardiac MR and echo in late survivors of combined modality therapy for lymphoma.

**Method:** 20 patients were recruited for cardiac screening. All had completed combined modality therapy for lymphoma more than 8 years previously, were currently in remission and did not have known heart disease or significant risk factors other than previous therapy. Each completed risk questionnaire, and had ECG, echocardiogram, cardiac MR and serum BNP checked.

**Results:** 5 men, 15 women were recruited. Age range at time of study 25-58 years (median 40) with time since last treatment of 8-20 years (median 10). 5 patients had DLBL and 15 Hodgkin's (HD), with 7 of the HD having had relapses and further treatment. Radiotherapy doses ranged from 30-45 Gy. Five patients had mantle radiotherapy. Adriamycin doses of 150-450mg/m2 were given. 4 patients were ex-smokers with 3 current smokers. Echocardiogram in all 20 was reported as normal, as was ECG. Serum BNP results also were within normal range. Cardiac MR detected clear signs of reduced ejection fraction in 5 patients who were referred on to cardiology department.

**Conclusion:** As expected echocardiogram did not detect reduced cardiac function in asymptomatic patients. Our hypothesis that serum BNP might identify these patients has not been confirmed. Cardiac MR however does detect early changes ahead of other methods. We intend to further evaluate the cardiac MR with respect to coronary arteries, sites of cardiac damage and relation to radiotherapy fields.

## 456 THE IMPACT OF ADDITION OF RITUXIMAB TO CHEMOTHERAPY ON INCIDENCE OF CENTRAL NERVOUS SYSTEM RELAPSE IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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**Introduction:** The addition of rituximab to CHOP (cyclophosphamide, doxorubicin, vincristine and prednisolone) was proved to improve remission rate, event-free and overall survival of patients with diffuse large B-cell lymphoma (DLBL). We evaluated the impact of rituximab on the incidence of central nervous system (CNS) relapse in the DLBL patients in a local hospital in Hong Kong.

**Method:** Patients aged 18 or above with DLBL patients diagnosed from January 1997 to December 2009 were identified. They were recruited into the study if they were treated with CHOP or R-CHOP with curative intent. They had a minimum follow-up of 12 months. CNS involvement was defined as either the presence of malignant lymphoma cell in the cerebral spinal fluid (CSF) or typical imaging result in magnetic resonance imaging or computerized tomography. The rate of CNS relapse was compared in the two groups. Incidence and risk factors for CNS relapse were also identified.

**Results:** A total of sixty-nine patients were recruited in the study. Thirty-six patients (52%) received CHOP and thirty-three (48%) received R-CHOP. The baseline characteristics of the two groups were similar. The median age was 55 and 49 in the CHOP and R-CHOP groups respectively. There were a total of seven CNS relapse with incidence 10.1% in the study. The incidence of CNS relapse was 11.1% in the CHOP group and 9.1% in the R-CHOP group. There was no significant difference between the groups.

The significant risk factors identified for CNS relapse included stage IV disease (p=0.001, Fisher's exact test), bone marrow involvement with lymphoma (p=0.015) and lactate dehydrogenase (LDH) level three times above upper limit (p=0.019).

**Conclusion:** The addition of rituximab did not appear to decrease the risk of CNS relapse in patients with diffuse large B-cell lymphoma in this study.

## 457 RITUXIMAB, GEMCITABINE AND OXALIPLATIN (R-GEMOX) IN THE TREATMENT OF RELAPSED OR REFRACTORY LYMPHOMA: THE EXPERIENCE FROM A SINGLE CENTRE

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**Introduction:** The treatment of relapses of non-Hodgkin Lymphoma (NHL) in the era of Rituximab (R) is very difficult. Most of the regimens available are remarkably toxic

requiring hospitalization with frequent complications. According to previous experience with the combination of R with Gemcitabine (GEM) and Oxaliplatin (OX), we decided to start at our institution a prospective open phase II trial, including all NHL CD20 + refractory and/or relapsed, to determine the efficacy, toxicity, the possibility of harvesting hematopoietic progenitors and the feasibility in an outpatient basis.

**Methods:** We treated from JAN 09 to DEC 10 refractory and relapsed NHL CD20+ with R-GEMOX: R-375mg/m$^2$iv, D1; GEM-1000mg, infusion rate of 10mg/m$^2$/min, iv D2; OX-100mg/m$^2$, iv, D2,14/14 day cycles, maximum of 6 cycles. We treated 21 patients, 13 woman, median age of 64 years (range 25-76), median time from diagnosis of 25 months (range 1-114), Type (Diffuse/11; Follicular/3; Mantle Cell/4; Lymphocytic/1; Marginal zone/1; Other/1), Ann-Harbor (I/1; II/4; III/6; IV/10), IPI (1/2; 2/5; 3/5; 5/2); FLIPI (1/1; 2/1; 3/1), MIPI (1/2; 3/2), ECOG (0/5; 1/14; 2/2), 11 in the 1st relapse, 6 in the 2nd and the other ones with 3 or more lines. We followed the recommendations of the Response Criteria in malignant lymphomas of the IWG.

**Results:** We evaluated the response in 21 patients: CR-8 (38.1%), PR-2 (9.5%), SD-2 (9.5%) and PD-9 (42.9%). Four patients had neurotoxicity to OX requiring dose reduction in 1 patient and lowering the perfusion rate in the other 3; Eight infectious complications, 6 respiratory with only one hospitalization. We performed 6 autologous stem cell transplant and 1 allogeneic. The median time of follow-up was 6M (range 2-21M), 6 patients died: 4 with PD, 1 with severe respiratory infection and 1 for Pulmonary Aspergillosis and GVHD after allogeneic transplantation. The remaining patients with PD are in rescue treatments.

**Conclusions:** The R-GEMOX was feasible in ambulatory regimen with acceptable toxicity, allowed the harvest of hematopoietic progenitors in all proposed patients (5) and had an appreciable efficacy if we consider the characteristics of patients included (Overall Response = 47.6%).

## 458 TUNISIAN EXPERIENCE IN THE TREATMENT OF AGGRESSIVE NON HODGKIN'S LYMPHOMA IN ADULTS: ABOUT 337 PATIENTS

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From January 1997 to December 2005, 337 patients with aggressive non Hodgkin's lymphoma were treated with one of the two successive multicentric non randomized protocols established in Tunisia. The mean age was 53 years. Most patients had diffuse large cell lymphoma with B phenotype in 86 % and T in 14 %. The performance status was 2 or 3 in 34 % of cases. The LDH were elevated in 74 % of cases. Advanced disease (III or IV stage) was noted in 59 % of cases and 10 % had a tumoral mass greater than 10 cm. According to the international prognostic index (IPI) ajusted to age, we distinguish four groups: group 1(0 factor and age < 70 years), group 2 (1-3 factors and age ≤ 60 years), group 3 (1-3 factors and age between 61 and 70 years) and group 4 (1-3 factors and age > 70 years). The patients of group 1 (n=47) received 3 courses of CHOP regimen followed by irradiation. The patients of group 2 (n=160) received 4 courses of ACVBP regimen (+ Rituximab for 21 patients) followed by consolidation (n=92) or peripheral blood progenitor cell transplantation (n=20). The patients of group 3 (n=61) received 8 courses of CHOP regimen (+ Rituximab for 20 patients). The patients of group 4 (n=69) received 6 courses of miniCEOP regimen (n=48) or 6 courses CVP regimen (n=21). The 4-year overall survival was 56 % and the 4-year event free survival was 49 %.

## 459 OUTCOME OF ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: A SINGLE INSTITUTION EXPERIENCE

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**Introduction:** Diffuse large B-cell lymphoma (DLBCL) is the most common type of malignant lymphoma. Although the outcomes are considered to be worse among elderly, than among younger patients with DLBCL, elderly patients are often less intensively treated in the clinical setting because of comorbidities and diminished organ functional reserve. Since few reports have described the true outcomes of patients aged ≥ 70 years with DLBCL in the clinical setting, we investigated the outcomes of this population treated at our institution.

**Methods:** Results from all (n = 100) patients with a median age of 77 years (range, 70 – 89 y; male, 44%) with recently diagnosed DLBCL who visited our institution between January 2002 and May 2010 were retrospectively analyzed.

**Results:** Among the patients, 27% of them had poor performance status (PS) scores of 3 and 4 and 51% had International Prognostic Index (IPI) scores of 4 - 5. Comorbidities included cardiovascular disease (27%), hypertension (41%), diabetes mellitus (16%) and other types of cancer (24%), and R-CHOP was administered to 93% of them. Overall, 68% of the patients achieved complete remission (CR), with a median follow-up of 38.7 months. Among 36 who died, 19, 13 and 4 were due to lymphoma-related, non-lymphoma-related and unknown causes. Two deaths were associated with therapy (generalized peritonitis and pneumonia). Multivariate analysis revealed that IPI score (RR = 12.1 for non-low vs.low; 95% CI 2.9 - 50.2) and number of chemotherapy cycles (RR = 4.3 for ≤ 5 vs. ≥ 6; 95% CI 1.3 - 14.7) significantly influenced CR. The estimated 5-year overall survival (OS) rates were 55.2% (95% CI, 42.7-67.7). Absolute lymphocyte count/R-IPI (ALC/R-IPI) score (HR = 15.8 for high vs.low; 95% CI, 5.1-48.7) and number of chemotherapy cycles (HR = 7.7 for ≤ 5 vs. ≥ 6; 95% CI, 3.5-17.0) were independent prognostic factors for OS in the multivariate analysis.

**Conclusions:** Even though the dose was actually reduced for some of these patients and others were not treated because of their overall health status, at least six cycles of R-CHOP were very important to improve the outcomes of this population. Adequate doses of R-CHOP should be administered to both elderly and younger patients with DLBCL.

## 460 OUTCOME OF ELDERLY NHL PATIENTS TREATED WITH CONVENTIONAL SECOND LINE PROTOCOLS FOR RELAPSE

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**Introduction:** Diffuse large B-cell lymphoma is the most common type of non-Hodgkin's lymphoma (NHL). Median age at diagnosis is 65 years, up to 35% of patients are older than 70 at diagnosis. Identification of suitable treatment options for older patients is assuming greater interest.

Recent studies show the best way to improve survival of older patients is to administer an optimal chemotherapy regimen, and first line CHOP and Rituximab is now the gold standard for aggressive lymphomas in older patients. Few series have been dedicated to the treatment of relapsing older patients. In most series the upper age limit is 65-70 and outcome of the elderly is not specifically mentioned. In this study we retrospectively review the clinical features, treatment and outcome of patients older than 70 with relapsed or refractory disease that received conventional salvage regimens.

**Methods:** Records of patients older than 70 with NHL and treated in 2000-2009 were reviewed. Patients with relapsed or refractory disease were included. Chemotherapy given, dose intensity, complications and response were recorded. Second line protocols were divided into aggressive (platinum- based) and non aggressive (all others). Outcome was defined by complete remission (CR), time to progression (TTP) and Overall survival (OS).

**Results:** 32 patients were included. Median age at diagnosis was 72. 1$^{st}$ line chemotherapy was CHOP in 43.8% and R-CHOP in 34.4%. CR rate was 71.9%. 10/32 patients were refractory to 1$^{st}$ line chemotherapy. Median time to 1$^{st}$ relapse was 24.5 months and median age at 1$^{st}$ relapse was 74. All patients received at least one line of salvage. 96.9% received aggressive chemotherapy.

CR rate after 2$^{nd}$ line chemotherapy was 40.6%. Median time to 2$^{nd}$ relapse was 31.3 months. CR rate was 42.3% in patients receiving aggressive chemotherapy regimens and 33.3% in those receiving non aggressive regimens. Patients receiving an aggressive protocol had longer TTP- 42.2 months vs. 18.7 months. Median OS was 32 months. Most common complications were sepsis and neutropenic fever. 40.6% and 59% of patients were hospitalized due to complications after 2$^{nd}$ and 3$^{rd}$ lines of chemotherapy respectively.

18 /32 patients died- 2 due to sepsis and 16 due to Lymphoma progression.

**Conclusion:** Salvage therapy for refractory/ relapsed aggressive lymphoma in elderly patients is feasible. 42.3% of patients achieve a 2$^{nd}$ CR with median TTP of 42.2 months and median OS of 32 months.

The best way to improve outcome of elderly patients with relapsed/refractory aggressive lymphoma is to administer the same salvage therapy as younger patients.

## 461 RITUXIMAB IMPROVES QUALITIY OF RESPONSE AND SURVIVAL IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): A POPULATION-BASED STUDY

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**Background:** CHOP-rituximab has become the standard of treatment of DLBCL elderly patients based on the GELA trial LNH-98-5. However, whether these results are reproducible in our daily practice is still a matter of interest. We decided to analyse the outcome of patients over 65 treated at our institution with conventional chemotherapy compared with those receiving rituximab combined regimens.

**Patients and Methods:** we included 106 patients consecutively diagnosed of DLBCL at our institution between January 1990 and June 2010 and who received active treatment. Median age was: 74 years (range, 65 to 96), Male sex 46 (42%). Bulky disease was present in 43 (39%), PS≥ 2, 34 (31%), Ann-Arbor stage I 25 (23%), II (30%), III (28%), IV (27%), increased LDH 46 (43%), increased beta2-microglobulin (UNL) 40 (36%), ≥ 1 extranodal sites 14 (13%) and IPI ≥ 3, 43 (39%). 61 (56%)patients received

conventional chemotherapy with anthracycline-containing regimens (group A) whereas 45 (41%) patients were treated with a rituximab-containing regimen, mainly CHOP-R (group B). Mean characteristics of both cohorts (pre and postrituximab) did not show statistical significance except for LDH levels which were higher in the rituximab cohort (A: 32% versus B: 61%, p=0.005)

**Results:** Median follow-up of the alive patients was 45.7 months (0.8 to 157.3). 76 out of 103 (74%) achieved a complete remission, 41 out of 58 (71%) in rituximab-naïve patients and 34 out 44 (77%) in the rituximab-treated ones. Median time to progression (TTP) was 49 months (95%CI 24,73) in group A and not reached in group B. Median overall survival was 60.75 months 95% CI (20.4, 101.1) in group A and 92 months (67.1, 117) in group B (p= 0,09). Considering lymphoma-specific mortality, 68% of group A were alive at 48 months compared to 91% (p=0,01) of group B. Main clinical variables identified in multivariable analysis for TTP and survival were treatment with rituximab (HR 0.2 95% CI 0.07, 0.52) and (HR 0.16 95%CI (0.04, 0.69) respectively (p=0.001), and IPI score ≥ 3, HR 2.59 (1.28, 5.23) and3.33 (1.24, 8.92)(p=0.008).

**Conclusions:** In our experience, rituximab in combination with chemotherapy improves the quality of response and both, overall and lymphoma-specific survival in our elderly lymphoma population. Combination of CHOP-rituximab allowed to complete the whole course of treatment compared to more intense chemotherapy schedules previously used.

## 462 RARE FORMS OF PRIMARY EXTRANODAL NON-HODGKIN'S LYMPHOMAS: DISTANT RESULTS AFTER I LINE THERAPY (EXPERIENCE OF ONE RUSSIAN CENTER)

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**Aim:** Extranodal NHL is rare disease (1,1%-10% of all NHL). The aim of our review were determination and comparing of distant results after I line therapy of several type rare extranodal NHL: thyroid, parotid, testis, bone.

**Materials and Methods:** 708 patients with primary extranodal NHL were observed in CRC of RAMS sins 1983 to 2007. More rare forms in 235 cases (33% of all extranodal NHL) were exposed by us. diagnosis was determined after ectomy, resection or open biopsy of the tumor with following immunohystochemical method investigation.

**Results:** 39 patients (pts) (16,6%) were affected by primary NHL of thyroid gland. Median of follow up-59 months (mnts). Histological type: diffuse large B-cell lymphoma (DLBCL) - 27 (69,2%) pts. Early stages - in 61%: IE-28%, IIE-33%. Therapy: CHOP+/-R-21 - 24 caes (61,5%), chemoradiotherapy (summary dose - 34-38 Gy) - 8 (20,5%). Median of overal survival (OS) - 38 mnts. OS: 1 year-79%, 3 year - 52%, 5 year - 37%. Disease free survival (DFS): 1 year - 57%, 3 year-32%, 5 year-25%. Parotid gland NHL-44 cases (18,7%). Median of follow up - 74,2 mnts. Histological type: DLBCL-41%, MALT-lymphoma- 39%. Early stages-in 66%: IE-34%, IIE-34%. Therapy: CHPO+/-R-21 - 29 (66%), chemoradiotherapy (SD 34-42 Gy) - 16 (36%). median of OS -91 mnts. OS: 1 year-92%, 3 year- 80%, 5 year-71%. DFS: 1 year-88%, 3 year-74%, 5 year-47%. NHL of testis - 62 pts (26%). Median of follow up - 30 mnts. DLBCL-60 (97%). Quantity of early and advance stages were the same: IE-35,5%, IIE-14,5%, III-19,3%, IV-30,7%pts. Therapy: CHOP+/-R-21 - 40 (64,5%), chemoradiotherapy (SD 44-60Gy) - 6 (9%). Median of OS 18 mnts. OS: 1 year - 67%, 3 year - 29%, 5 year - 17%. DFS: 1 year - 48%, 3 year - 22%, 5 year - 12%. NHL of bones-90 (38%) cases. Median of follow up - 60,3 mnts. DBLCL - 65 (83,3%). Quantity of early and advance stages the same: IE-41%, IIE-5,6%, III-4,4%, IV-49% pts. Therapy: CHOP+/-R-21 - 35 (39%), chemoradiotherapy (SD 46-48Gy) - 44 (49%). Median of OS - 49 mnts. OS: 1 year-85%, 3 year - 54%, 5 year - 44%. DFS: 1 year - 63%, 3 year - 52%, 5 year - 43%.

**Conclusions:** the favourable prognostic group was lymphoma of parotid gland (median of OS 91 mnts, OS 5 year - 71%, DFS 5 year - 47%), primary lymphoma of testis was delivered to poor prognostic group (median of OS 18 mnts, OS 5 year - 17%, DFS 5 year - 12%).

## 463 PLATINE AND CYTARABINE-BASED SALVAGE TREATMENT FOR PRIMARY CENTRAL NERVOUS SYSTEM LYMPHOMA

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**Introduction:** up to 35% of patients with primary central nervous system lymphoma (PCNSL) are refractory to or relapse after first-line chemotherapy. In our previous experiences, patients failing to high dose methotrexate -based chemotherapy received a salvage treatment by CYVE (high-dose cytarabine and etoposide) and a consolidative intensive chemotherapy and hematopoietic stem cell rescue (IC + HCR) combining thiotepa, busulfan and cyclophosphamide (1,2). Best results were observed in patients who were chemosensitive to CYVE and who received the IC + HCR but we observed around 10% rate of treatment-related death after CYVE. In this study we evaluate the efficacy and toxicity of two chemotherapy regimens based on platinum and cytarabine in association with etoposide and methylprednisolone (ESHAP) or with dexamethasone (DHAP) with or without rituximab (±R) in patients with refractory or relapsed PCNSL.

**Methods:** consecutive patients from two French centers with refractory or relapsed PCNSL treated with ESHAP/DHAP ± R were included. We analyzed the overall response rate (ORR), toxicity and overall survival (OS) after salvage chemotherapy. IC + HCR was offered to patients <65 years of age. These results were compared with two previously reported series of PCNSL patients treated with the CYVE regimen at relapse.

**Results:** twenty-two patients received a total of 60 DHAP/ESHAP cycles (median 3; range 1-5). The median age was 59 years. The orr after salvage chemotherapy was 59%. Toxicity was mainly hematological, 18% of patients showing febrile neutropenia. There was no treatment-related death.

**Conclusions:** ESHAP or DHAP regimens led to similar ORRs compared to the CYVE regimen in relapsed or refractory PCNSL, although they seemed less toxic. The therapeutic results of the ESHAP/DHAP regimens in relapsed or refractory PCNSL were also similar to those for relapsed systemic non-Hodgkin's lymphomas. Both chemotherapies, CYVE regimen and ESHAP/DHAP are treatment options to be considered in relapsed or refractory PCNSL, especially when IC+HCR is planned as a consolidation treatment.

## 464 RELAPSE PATTERN AND PROGNOSTIC FACTORS OF PRIMARY CNS LYMPHOMA

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**Background:** The aim of this study was to evaluate the pattern of relapse and investigate prognostic factors for PCNSL with a single institution experience.

**Methods:** Between November 1995 and August 2010, 70 patients with newly diagnosed PCNSL at the Asan Medical Center, Seoul, Korea were included.

**Results:** The median age was 54.5 years (range, 26-77 years) and 55 (78.6%) patients had intracranial lesions only. Nine patients had leptomeningeal involvement, 2 had ocular lesions, and one had spinal cord lesion. Only 3 patients had systemic lesions; bone marrow, muscle, and lymph nodes. Thirty-one patients (44.3%) were treated with chemotherapy only, 13 (18.6%) with chemotherapy followed by whole brain radiotherapy (WBRT), while 21 (30.0%) were given HDC followed by ASCT. Two patients received palliative WBRT only and 3 received best supportive care. While all patients achieved CR (complete response, 76.2%) or PR (partial response, 23.8%) with ASCT, overall response rate (ORR) to chemotherapy and chemotherapy followed by WBRT were 64.5% and 84.6%, respectively. No systemic relapse was noted among 27 patients experiencing relapse; intracranial lesion only in 23 patients, 3 with leptomeningeal involvement and one with ocular relapse. Median overall survival (OS) and failure free survival (FFS) of all patients were 35.8 and 13.1 months, respectively. Age< 60 years (44.9 ± 12.41 versus 27.0 ± 6.93 months, p=0.040) and Eastern Cooperative Oncology Group performance status (PS) < 2 (44.9 ± 12.41 versus 13.2 ± 13.81 months, p=0.002) were the only variables related to prolonged OS. Other variables in the International Extranodal Lymphoma Study Group prognostic scoring system and Memorial Sloan-Kettering Cancer Center prognostic model were not predictors of survival in this group. Patients received ASCT had longer OS (58.6 ± 21.48 versus 33.3 ± 8.65 months) but without statistical significance (p=0.083), while they had significantly better FFS (35.5 ± 19.83 versus 9.9 ± 2.96 months, p=0.013).

**Conclusions:** Considering no systemic involvement of relapsed PCNSL in current study, regular evaluation with computed tomography or positron emission tomography to investigate extracranial sites might not be necessary in PCNSL patients. Age and PS still retain prognostic significance irrespective of treatment scheme, and ASCT could lead to improve response rate and FFS.

## 465 WHOLE BRAIN RADIOTHERAPY (WBRT) FOLLOWED BY CHOP CHEMOTHERAPY IS STILL A VIABLE OPTION FOR PRIMARY CNS LYMPHOMA IN LOW RESOURCE COUNTRIES

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**Background:** Primary CNS Lymphoma (PCNSL) is an uncommon malignancy with potentially aggressive behavior. To access the management strategies and outcome of PCNSL in routine clinical setting, a retrospective study has been performed in the Department of radiotherapy, a tertiary care institute of north India.

**Material and Method:** Between January 2004 and May 2010 a total 39 patients of PCNSL were treated. Thirty-two patients had histologically proven while 7 patients diagnosed radiologically. After routine investigations, all patients received WBRT, followed by chemotherapy with CHOP regimen. Bi-weekly intrathecal methotrexate was given in patients having CSF spread till it came out to be negative.

**Result:** Out of 39 patients, 20 (51.3%) were males. The patients had a median age of 53.0 yrs (Range: 30-75 yrs). Frontal lobe was the most commonly involved sub-site in 14 (36%). Complete resection was done in 8 patients, CSF cytology was positive in 5 patients. All patients received WBRT first followed by systemic chemotherapy with standard CHOP regimen to total 6 cycles at 3 weekly intervals. Radiotherapy dose was 36-40 Gy in 20 fractions. Overall compliance was excellent as 37 (94.9%) patients completed planned treatment without any break. Significant acute reactions as per RTOG grading Criteria were skin Grade III in 3, anemia grade II in 2, leucopenia Grade II in 2 patients only. At 1 month MRI revealed no residual in 22 patients. No treatment related mortality encountered.

Survival analysis was performed using Kaplan Meier (KM) method that demonstrated mean overall survival (OS) 36.34 months, median OS 18 months with 3-year actuarial OS of 37%. Impact of KPS of the patient was also included into KM survival individually as well as after stratification of the data on age & sex respectively. The result shows that survival seems to be unaffected by KPS. Cox regression analysis using KPS, age as continuous in nature along with gender demonstrate mean age of 50 years significant ($p = 0.05$) prognostic factor.

**Conclusions:** Treatment of PCNSL with high dose chemotherapy under clinical trial setting definitely has better outcomes. Considering poor compliance to treatment and Lack of infrastructure in low resource country like India, in routine clinical setting WBRT followed by CHOP chemotherapy demonstrate reasonably good outcome which is quite economic as well as simple to implement.

## 466 HIGH-DOSE METHOTREXATE, TEMOZOLOMIDE AND INTRATHECAL LIPOSOMAL CYTARABINE (HD-MTX-TMZ-IT LC) WITHOUT RADIOTHERAPY FOR PRIMARY OR SECONDARY CENTRAL NERVOUS SYSTEM (CNS) LYMPHOMA

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**Background:** CNS lymphoma is an aggressive tumor. Combined systemic chemotherapy-radiotherapy may be associated with acute and/or delayed neurotoxicity. HD-MTX-TMZ appears to be an effective and relatively safe regimen. Adding IT LC may further improve therapeutic efficacy. We report our preliminary experience with HD-MTX-TMZ plus IT LC used upfront or as salvage in 4 CNS lymphoma patients.

**Material and Methods:** Induction: MTX 3g/ms IV d 1, 10, 20, TMZ 100 mg/ms d 1-5; maintenance (≥SD pts): MTX 3g/ms d 1, TMZ 100 mg/ms d 1-5, every month up to 5 cycles as long as response was documented. Fifty mg IT LC was given concomitantly, at least 14 days apart and at least 7 days from HD-MTX, up to 6 doses.

**Results:** pt 1, 56 y, male, testicular diffuse large B cell lymphoma (DLBCL), stage IVA, cerebellar relapse after CR, Karnofsky performance status (KPS) 50%. Rituximab-TMZ and IT MTX were initiated but soon discontinued due to CMV pneumonia. After recovery, HD-MTX-TMZ was started and precautionary stem cell harvest performed. Six cycles and 4 IT LC injections were given with no G3-4 toxicities. He obtained CRu. Pt 2 76 y, male, primary CNS peripheral T-cell lymphoma not otherwise specified, multicentric, KPS 60%. He was treated with steroids and TMZ, but progressed in 3 months. He received 6 HD-MTX-TMZ cycles with 4 IT LC injections. G2 renal insufficiency and G3 steroid-induced diabetes mellitus were reported. He obtained CRu. However, 7 months later he relapsed in involved sites, received 2 further cycles of TMZ and is now in SD. Pt 3,68 y, female, PCNSL, DLBCL, left cerebellar hemisphere, KPS 50%. HD-MTX-TMZ and concomitant IT LC were initiated as first-line. G3 atrial fibrillation was reported. Maintenance was completed. After the 5$^{th}$ IT LC injection she developed conus-cauda equina syndrome and IT therapy was withdrawn. She obtained very good PR after induction. Pt 4, 71 y, female, DLBCL stage IIIE (i.e. subcutaneous facial localization), with multicentric bilateral subcortical relapse. Four HD-MTX-TMZ cycles and 5 IT LC injections have been given so far, with no neurotoxicity. CR was attained after induction and sustained thereafter.

**Conclusions:** HD-MTX-TMZ-IT LC therapy appeared feasible and effective, even in elderly pts. CR/CRu was attained in 3/4 pts. Response duration was 18+, 7, 10+, and 5+ months in pts 1, 2, 3 and 4, respectively. Conus-cauda equina syndrome is a known complication of IT chemotherapy via lumbar puncture. Follow-up is too short to make comments on delayed neurotoxicity.

## 467 LONG TERM FOLLOW UP OF LOCALIZED, PRIMARY GASTRIC DIFFUSE LARGE B-CELL LYMPHOMA TREATED WITH RITUXIMAB AND CHOP

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**Introduction:** Addition of rituximab to cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), i.e., R-CHOP is considered as the standard regimen for treating localized, primary gastric diffuse large B-cell lymphoma (PG-DLBCL). However, few studies reporting the long-term efficacy of R-CHOP therapy in the management of localized PG-DLBCL have been published.

**Material and method:** We performed a retrospective analysis of 14 patients with localized PG-DLBCL treated with R-CHOP at Nihon University Itabashi Hospital and Kasukabe Municipal Hospital from 2001 to 2010. Limited stage cancer was defined as stage I/II according to the Lugano staging system for gastrointestinal (GI) lymphomas.

**Result:** The median age of patients was 68 years (range 48–82). Gastralgia and anemia were common symptoms at initial presentation. All patients except 1 received 6 cycles of R-CHOP treatment without consolidative radiation therapy or prior surgery. All patients achieved complete remission, and the estimated overall survival with a median follow-up of 46 months (range 7–92) was 100% without relapse or significant GI adverse effects such as perforation or bleeding during R-CHOP treatment. No long term adverse effects of rituximab were recorded during the observation period. Helicobacter pylori infection was diagnosed in 78.5% of patients, but was eradicated in a limited number of patients.

**Conclusions:** Our results investigate the feasibility and effectiveness of the addition of rituximab to conventional CHOP therapy in the management of localized PG-DLBCL.

## 468 PRIMARY EXTRANODAL LYMPHOMAS OF LIVER (PELL): CLINICAL, DIAGNOSTICS AND TREATMENT

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PELL as the primary tumour meets seldom. In literature all PELL was non Hodgkin's lymphomas (NHL). PELL is 0,4 % of all NHL. Diffusive B-cells lymphomas (DLDCL) compound to 96 % of all PELL. At 60 % of patients PELL has one solid tumor, at 35 % - many solid tumor, at 5 % diffusively amazes a liver. On a lobe follicular lymphomas is only 4 % of PELL. The forecast at PELL is bad.

Diagnostic criteria are not defined now.

In Russian Academies of Medical Science from 144 pts with primary tumor of liver have been taped 16 pts with PELL. Biopsies of tumour of liver in our research it was made by all pts. All diagnoses PELL confirmed by histological and immunohistochemical research of tumor. The age median was 51 years. Men there were 14 women 2. DLBCL were at 14 lymphomas and follicular lymphomas were at 2 pts. The solid lesion of a liver was at 15 patients, and one diffusive. One solid tumor was at 6 of 15 pts. The HCV was 9 pts, HBV - at 2 pts. Serum level HCV RNA and HBV DNA was very high. Median serum level HCV RNA consist $6.8 \times 10^6$. AFP at all pts was increased from 10 to 50, median 20.4, CEA was normal at all, and LDG increased at all and fluctuated from 5 to 20 norms. Level ALT and AST was increased from 3 to 35 norms. At pts with hepatitis level ALT and AST was authentically above. At patients without a virus hepatitis of AST was above than ALT, at patients with HCV/HBV ALT was above AST. In bunch of pts with hepatocellular carcinoma (HCC) the age median has compounded 65 years. HCV has been taped at 56 pts, at 52 - HBV, from them at 18 was hepatitis B+C. Cirrhosis was taped at 103 pts. AFP increased at all pts and fluctuated from 31 to 66000 IU -median 21000 IU. CEA also has been increased and fluctuated from 3 to 20 norms. Level LDG has been increased at 81 patients. Median of LDG was 1.5 norms. In all cases PELL at R-tomograph with contrast tumor of all pts with PELL was gipodensisity.

To pts with PELL chemotherapy CHOP- 9 pts R-CHOP-6 pts. 1 pts resection of a liver was made. Complete remissions have been reached only at 3 pts, partial remissions - at 10 pts, 3 pts- without effect. The median without recurrent survival rate compounds at CR-18 months, PR - 7 months.

In our research we can conclusion that pts with PELL have high level of LDG, normal level of AFP and CEA, in R-tomograph with contrast PELL all gipodensisity.

## 469 CLINICAL AND MORPHOLOGICAL CHARACTERISTICS OF PRIMARY NON-HODGKIN'S OF PAROTID GLAND LYMPHOMA ASSOCIATED WITH SJOËGREN'S SYNDROME (ONE RUSSIAN CENTER EXPERIENCE)

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Primary parotid gland lymphoma is a rare disease (2,5-7% of all extranodal NHL). The aim of our study were examination of clinical and hystopathologic characteristics of this type lymphoma assotiated with Sjoëgren's syndrome.

**Matherials and methods:** In CRC of RAMS since 1983 to 2007^ 44 patients (6,2%) were affected by primary lymphoma of parotid gland. Diagnosis was proved by immunohystochemical method investigation of tumor.

**Results:** Median of follow up was 59 months. Female/male ratio: 29/10. Age ranged from 15 to 83 years (the median - 51 year). 26 patients (66,7%) were younger 60 age. The association Sjoëgren's syndrome and lymphoma has been found in 4 cases of female (10,2%). NHL was diagnosed after Sjoëgren's syndrome in 10 and more years; age range 55 - 64 years. Prognosis and efficacy of the I line therapy were poor when NHL associating with Sjoëgren's syndrome vs NHL de novo: bulky disease expose in 75% vs 54%, Burkitt's lymphoma - 25% vs 10%, ECOG 3-4 mark - 75% vs 45%, B-symptoms more frequently when Sjoëgren's syndrome was found - 50% vs 35%, level of Hb less 12g/l was 50% vs 41%. Efficacy of the I line therapy - RCHOP-21 - was poor in cases of

association Sjoëgren's syndrome and lymphoma: complete remission consists 25% vs 52% when this syndrome was not found; early recurrent of disease was in 3 of 4 patients (75%) from 1 to 5 months (2 of there dissemination recurrent) and early death - 3 cases.

**Conclusion:** preliminary data confirm that association Sjoëgren's syndrome and lymphoma has poor prognosis and it is necessary more investigation.

## 470 RAPIDLY EXPANDING NECK MASS: CONSIDER THYROID LYMPHOMA!

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**Background:** Thyroid lymphoma is a rare clinical entity accounting for 0.2% of thyroid cancers in Ireland. It commonly presents with a rapidly enlarging neck mass. The aim of this study was to review our experience of thyroid involvement by lymphoma.

**Methods:** A retrospective review of lymphoma referrals over a 12 year period (1998-2010), identified 12 cases of thyroid involvement. Patient demographics, clinical presentation, investigations, staging, diagnosis, treatment, and outcomes were assessed.

**Results:** Of the 12 patients, 11 were female. The median age was 69 years (range 22-82 years). Forty six percent presented with a symptomatic neck mass. Median duration of symptoms at presentation was 2 months. Thyroid dysfunction was seen in 75% of patients. On histological review, 9 patients had diffuse large B cell lymphoma, 2 had follicular lymphoma, and 1 had Hodgkin's lymphoma. Eight of 12 patients presented with stage I/II disease. Seventy five percent of patients were treated with systemic chemotherapy and 25% received a combination of chemotherapy and radiotherapy. A complete response was seen in 8 (67%) patients and a partial response in 2 (17%) patients. Two patients are currently on treatment. Two (17%) patients underwent emergency surgery. The median overall survival was 37 months (6-149 months).

**Conclusions:** The differential for a rapidly enlarging neck mass includes thyroid lymphoma and anaplastic thyroid cancer, early diagnosis is essential to facilitate appropriate treatment. Successful outcomes may be achieved in patients with thyroid lymphoma.