182 BENEFIT OF ANTI-VIRAL AND PNEUMOCYSTIS CARINII PROPHYLAXIS IN PATIENTS TREATED WITH R-CHOP

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The value of anti-infectious prophylaxis for patients receiving R-CHOP is unclear. While the rate of grade 3&4 infections in elderly patients under (R)-CHOP is around 20%, we observed a higher rate of infections in patients receiving 12 dose-dense applications of rituximab in combination with 6 cycles of CHOP-14 in the first 20 patients treated within the DENSE-R-CHOP-14 trial of the DSHNHL [Pfreundschuh et al., Abstract ASH 2007, 789]. 7 out of 20 of these patients (35%; 95%-CI: 15; 59%) in the DENSE-R-CHOP-14 trial had grade 3&4 infections, most of them consisting of interstitial pneumonia, confirming other reports of interstitial pneumonitis associated with R-CHOP. Three of these 20 patients died of infections. In one patient CMV viremia suggested CMV-induced pneumonitis, and pneumocystis carinii was demonstrated in the bronchial lavage of a second patient. As a consequence, prophylaxis with acyclovir (4×400 mg per day) and cotrimoxazole (2 double-strength tablets twice per week) in addition to levofloxazine (day 7 to 12) was made mandatory for the remaining 80 patients in the DENSE-R-CHOP-14 trial. This resulted in a significant reduction of cycles with grade 3&4 infections in patients #21-100 compared to patients #1-20 (15/118 = 12.7% vs. 26/409 = 6.4%; p=0.023) and patients with grade 3&4 infections (7/20 = 35.0% vs. 14/75 = 18.4%). Even more important, none of the patients in the DENSE-R-CHOP-14 trial who actually receceived the prophylaxis died of infectious complications. The rate of 18.4% cycles with grade 3&4 infections in patients receiving the prophylaxis was also considerably lower than the 24.6% in 32/130 patients of the RICOVER trial who received 6 cycles of CHOP-14 in combination with 8 bi-weekly applications of rituximab, despite the more favourable risk profile of the RICOVER-60 patients.

Conclusions: These results show a benefit of anti-infectious prophylaxis in patients receiving R-CHOP. Because the described prophylaxis is well tolerated and inexpensive it should be recommended to all elderly patients receiving R-CHOP.

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183 LAMIVUDINE PROPHYLAXIS IS EFFECTIVE FOR INHIBITION OF HEPATITIS B VIRAL REACTIVATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA UNDERGOING R-CHOP LIKE THERAPY

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Background: In recent years, R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone) is a standard regimen for patients with diffuse large B-cell lymphoma (DLBCL). Although several studies have been reported, the patients with hepatitis B virus (HBV)-positive DLBCL have been excluded. So we don't know prognosis of the patients with HBV-positive DLBCL.

Objective: To determine the effect lamivudine prophylaxis on the rate of HBV reactivation, progression-free survival (PFS), and overall survival (OS).

Methods: We analyzed retrospectively the prognosis of HBV-positive DLBCL treated with R-CHOP like regimen, diagnosed at our single institute between July 2003 and June 2006. The pathology was reviewed by a hematopathologist and confirmed to be DLBCL according to the WHO classification. All patients with HBV-positive DLBCL started lamivudine prophylaxis before R-CHOP like therapy.

Results: 115 patients with DLBCL receiving R-CHOP like therapy at our single institute were enrolled in this study. Hepatitis B surface antigen (HBsAg)-positive were 8 (median age=65 yr) and HBsAg-negative were 107 (median age=64 yr) (p=.522). The median follow up of surviving patients was 24 months. CR rate between HBsAg positive and negative were 62.5% vs. 76.6% (p=.637), and overall response rate were 87.5% vs. 94.4% (p=.984), respectively. One of eight HBsAg-positive DLBCLs (12.5%) showed HBV reactivation, but his hepatic function improved. Nobody died of HBV-related fulminant hepatitis and acute hepatic failure. 2yr-PFS were 73.3% vs. 80.8% (p=.487), and 2yr-OS were 100% vs. 89.5% (p=.518), respectively.

Conclusion: These results suggest that lamivudine prophylaxis is effective for inhibition of HBV reactivation in patients with DLBCL undergoing R-CHOP therapy, and the prognosis of HBV-positive DLBCL is not inferior to HBV-negative DLBCL. We recommend lamivudine prophylaxis for patients with DLBCL undergoing R-CHOP therapy.

184 ARRAY-CGH IN DIFFUSE LARGE B-CELL LYMPHOMAS (DLBCL) TREATED WITH R-CHOP IDENTIFIES RECURRENT 11Q24.3 ABERRATIONS

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Background: DLBCL consists of heterogeneous group of tumors. More than 30% of cases are not cured with R-CHOP chemotherapy. To better characterize the molecular mechanisms, we performed an array CGH study on uniformly treated DLBCL patients.

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

Results: 73/200 samples have been analyzed to date. Minimally deleted regions have been identified in 1p36.22-36.23, 1p35.3, 1q22, 2p14-16.1, 3p21.31, 3q29, 6p21.1, 5p13.3-15.2, 6q15-q16.1, 6q23.3, 7p22.1, 7q11.21, 7q11.23, 7q22.1, 7q32.2, 9q34.11, 9q34.3, 11q13.1, 12q24.11, 12q24,31, 14q11.2, 14q32.35-32.33, 15q15.1, 16p13.3, 16p11.2, 16p22.1, 16q23.1, 17p13.3, 17q25.1, 19p13.3, 19q13. Minimally gained regions were at 1q23.3-25.1, 1q25.2, 1q31.3, 2p14-p16.1, 7q21.1-21.3, 11q24.3, 11q25, 12q14.1-15,14q32.33, 18q22.11-22.3. Concomitant analysis of DNA changes and genotype, showed uniparental disomy in 27% at 6p21.33 and 17% at 17q21.31-33. The 11q24.3 gain (8/72 cases, 11%) contained the genes coding for the transcription factors *ETS1* and *FLI1*, that have a role in lymphocyte development. Preliminary immunohistochemistry confirmed co-expression of both genes on cases with DNA aberrations. Analysys of the LLMPP dataset, via Oncomine, indicated that the genes expression in DLBCL is highly co-correlated (R=0.68). Since *ETS1* is downregulated in B-cell differentiation to plasma cells, therefore, a gain might maintain B-cells in the germinal center stage.

Conclusions: ArrayCGH identified new genomic lesions in DLBCL, suggesting further study may be valuable in one subset with gains on 11q24.3.

185 GENOMIC IMBALANCES ASSESSED BY ARRAY CGH IDENTIFIED PROGNOSTIC GROUPS IN PATIENTS WITH AGGRESSIVE DIFFUSE LARGE B-CELL LYMPHOMAS TREATED WITH MEGACHOP REGIMEN

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Aim: To study patients diagnosed as aggressive DLBCL by CGH-array to identify genetic factors as prognostic markers.

Patients and methods: Forty patients with IPI score >1 treated with dose-escalated CHOP followed by SCT were studied. The DNA of 22 specimens was isolated from the paraffin-embedded tumor material and the rest of samples were obtained from frozen cells. A total of 3429 genomic targets DNAs, BAC/PAC clones, were compounded from RP-11 libraries (Sanger Institute, Cambridge, UK) which were spaced approximately 1Mb. FISH studies with specific probes obtained from the same libraries were carried out in order to confirm the array data.

Results: DNA copy changes were observed in 95% of patients. The most frequent aberrations were gains on 11q23.3 (50%), 3p21.1 (48%), 6p21.1, 11q12 (45%), 12q13 (43%), 1q21 (40%), and 1q32 (38%) while genomic losses affected 5q21.1 (33%), 8q23.1, 11q14 (25%), 3q13 (23%), and 17p13.1 (18%). The genomic profile characterized a subgroup of 18 patients with 3p+, 6p+, 7p+, and 11q+. The patients not achieving a complete response with dose-escalated CHOP had gains on 2p and losses on 17p. In addition, the survival analysis only showed the age (> 60 years), the

losses on 10q and the losses on 17p as factors correlated with a short survival. In the Cox analysis only the age and the losses on 10q retained the prognostic value.

Conclusions: CGH-array provided comprehensive high resolution scanning of the DLBCL genome and identified multiple regions with common copy number changes. The age and the 10q deletion were correlated with shorter survival.

186 THE PROGNOSTIC SIGNIFICANCE OF A *MYC* GENE REARRANGEMENT IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: Approximately 5-8% of cases of diffuse large B-cell lymphoma (DLBCL) harbour a *MYC* gene rearrangement at diagnosis; however, the prognostic significance is largely unknown. A recent gene expression profiling study has suggested that the presence of breakpoints at the *MYC* locus in cases with a 'non molecular Burkitt's' profile is associated with a poor survival rate. However, this has yet to be validated using standard histologic diagnostic criteria for DLBCL or in patients treated with CHOP in combination with rituximab (CHOP-R).

Methods: A DLBCL tissue microarray (TMA) consisting of 142 newly diagnosed cases (CHOP treated n=72; CHOP-R treated n=70) was evaluated for the presence of a *MYC* rearrangement using a Vysis break-apart FISH probe. This information was linked to the BCCA center for lymphoid research clinical database to correlate the presence of a *MYC* rearrangement with clinical outcome.

Results: Eleven cases (7.7%) harboured a *MYC* rearrangement and had the following clinical features: Median age 71 (54-85); 64% male; 55% stage III/IV; 82% abnormal LDH; 27% ECOG ≥2; 55% bulky disease (> 10cm); 36% high risk IPI (4, 5). The 4 y overall survival was significantly worse in patients with a DLBCL tumour *MYC* rearrangement (60% vs 36% p=.006). Three patients had a central nervous system relapse. Multivariate analysis using Cox regression suggests that the prognostic impact of *myc* deregulation is independent of the IPI or treatment with rituximab (p=.012). There was a trend to a worse overall survival in cases which had an extra copy of *MYC* (n=60, p=.08).

Conclusions: Patients with DLBCL whose tumors harbour a *MYC* rearrangement have a significantly worse outcome, independent of the IPI or treatment with rituximab.

187 DIFFUSE LARGE B CELL LYMPHOMAS SHOW MAJOR PHENOTYPIC DIFFERENCES COMPARED TO NORMAL B-CELL COUNTERPARTS

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Introduction: Diffuse large B-cell lymphomas (DLBCL) have been sub-classified by comparing their expression profiles with those of normal B-cell subsets. The aim of this study was to investigate the phenotypic divergence between normal and neoplastic B-cells and to explore the application of this approach in improving diagnosis.

Methods: 20 reactive lymph nodes were stained using multi-colour immunofluorescence (MCIF) to define the normal expression profiles of CD10, BCL6, MUM-1 and FOX-P1. The in-house immunohistochemistry database was then interrogated in 1407 cases of DLBCL diagnosed from 2003 to 2007. Cases were classified as germinal centre (GC) or non-GC using Hans criteria and the phenotypic profile of each case defined as normal or aberrant, based on the findings of the reactive series. Finally, patterns of marker co-expression were further evaluated in 40 DLBCL using MCIF.

Results: In the GC of reactive lymph nodes, the following phenotypes were rare: any expression of BCL2 and co-expression of BCL6 and MUM-1(strong). In the non-GC component of reactive lymph nodes strong co-expression of either MUM-1 or FOXP1 with BCL6, or strong co-expression of MUM-1 and FOXP1 were rarely demonstrated. A deregulated P53 immunophenotype (P53+P21-) was classed as aberrant in all cases. 782/1407 (56%) cases of DLBCL had a GC phenotype and of these 767/782 (98%) phenotypes were aberrant. In the non-GC DLBCLs (44% of total cases) 567/625 (91%) cases were aberrant. Further analysis of a subset of DLBCL using MCIF showed that while the proportion of cells co-expressing combinations of BCL6, MUM-1 and FOXP1 was highly variable it was significantly greater than the normal range of co-expression in 37/40 (93%) cases.

Conclusions: This study shows that in the majority of cases of DLBCL, the neoplastic cells differ significantly from normal B-cells, which may reflect the underlying pathogenic mechanisms. This information can be exploited to improve the accuracy and confidence in the diagnosis of DLBCL particularly when only small samples are available. This is best carried out using MCIF which allows effective discrimination between co-expression of markers and multiple subpopulations of cells within the tumour.

188 BCL-2 BUT NOT FOXP1, IS AN ADVERSE RISK FACTOR IN IMMUNOCHEMOTHERAPY TREATED NON-GERMINAL CENTER DIFFUSE LARGE B-CELL LYMPHOMAS

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Background: Non-germinal center (non-GC) phenotype, transcription factor Forkhead box P1 (FOXP1) and anti-apoptotic protein Bcl-2 have been identified as unfavourable prognostic factors for diffuse large B-cell lymphoma (DLBCL) patients treated with chemotherapy. Given the fact that virtually all patients are presently treated with immunochemotherapy, there is a need to re-evaluate the prognostic value of these factors in DLBCL patients treated with rituximab (R) containing regimens.

Methods: GC and non-GC phenotypes and expression of FOXP1 and Bcl-2 were determined immunohistochemically from117 DLBCL patients treated with R-CHO(E)P. Expression data were correlated with survival.

Results: Consistent with previous studies on immunochemotherapy-treated patients, no prognostic impact of GC- and non-GC phenotypes on survival was found (FFS 80% vs 67%, P=NS, OS 86% vs 83%, P=NS). Expression of both FOXP1 and Bcl-2 was associated with the non-GC phenotype. For all patients no difference in outcome was observed between FOXP1 positive and negative patients (FFS 65% vs 75%, P=NS, OS 86% vs 84%, P=NS). However, Bcl-2 negative patients had a better survival than Bcl-2 positive ones (FFS 97% vs 61%, P=0.001 and OS 97% vs 78%, P=0.034). When the Bcl-2 related survival was analyzed separately in patients with GC and non-GC phenotypes, the adverse prognostic effect of Bcl-2 was seen only in patients with the non-GC phenotype. According to the International Prognostic Index the difference in survival between low- and high-risk patients remained significant.

Conclusions: Expression of Bcl-2 and FOXP1 are associated with non-GC phenotype, but only Bcl-2 predicts the survival of DLBCL patients treated with immunochemotherapy.

189 HIGH SKP2 EXPRESSION IS AN INDEPENDENT PREDICTOR OF UNFAVORABLE OUTCOME IN 684 PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA (DLBCL).

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We have reported that Skp2 expression in tumor cells is an unfavorable prognostic factor in DLBCL. In the present study, we investigated the significance of Skp2 expression in the patients with DLBCL treated with CHOP or CHOP-R. DLBCL patients (684 cases) were entered into this study, based on the availability of paraffin blocks for interpretable immunohistochemistry for all antigens (CD10, Bcl-6, MUM1, Bcl-2, Skp2, p27). All patients were diagnosed as having DLBCL at the twenty different hospitals and were treated with either CHOP (431) or CHOP-R (253) from 1996 to 2005. All specimens were histopathologically recomfirmed by one pathologist with expertise before entering into this study. Their clinical characteristics, including either the IPI or R-IPI factors, were evenly matched in both treatment groups. The median follow-up of living patients was 3.7 and 2.1 y for CHOP vs CHOP-R, respectively. DLBCL were assigned to GCB subtype (45.8%: 313/684) or non-GCB subtype (54.2%: 371/684) based on the method of Hans et al., with similar distribution in both treatment groups. High expression of bcl-6, p27, or GCB subtypes was associated with better overall survival (OS), whereas high expression of bcl-2 or Skp2 was associated with worse OS in CHOP treatment groups. The addition of R was associated with an improved survival in the non-GCB subtype and resulted in same as OS in GCB subtype. The survival benefit of both low Bcl-2 and high Bcl-6 expressions diminished in combined treatment with R to CHOP. There were 260 patients with high Skp2 expression (>40% positive cells) (260/684, 38.1%). High Skp2 expression is closely associated with the suppression of p27 and the aggressiveness in DLBCL treated with CHOP or CHOP-R. Interestingly, even in CHOP-R group, high Skp2 expression was the strong biomarker of worse prognosis. DLBCL patients with high Skp2 expression did not benefit from the addition of R to CHOP. Therefore, Skp2 may be a useful prognostic marker in recent rituximab era. The new treatment strategy is necessary for the DLBCL patients with high Skp2 expression.

190 EXPRESSION OF CD40 IS ASSOCIATED WITH PROLONGED SURVIVAL IN DIFFUSE LARGE B-CELL LYMPHOMAS: POSSIBLE ROLE OF EXTRACELLULAR MATRIX REMODELLING

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Introduction: We have recently shown that immunohistochemical expression of CD40, seen in approximately 70 % of diffuse large B-cell lymphomas (DLBCL), is associated with a prolonged overall survival. The data have been confirmed in an independent material. In order to elucidate the biological background for this effect, molecular profiling was applied.

Material: Gene expression profiles in tumour tissue from 96 patients with de novo DLBCL, stage I-IV, either CD40-positive (n=60) or CD40-negative (n=36), as determined by immunohistochemistry, were examined using spotted 55K oligonucleotide arrays. Immunohistochemistry was used for confirmation of gene expression data on the protein level.

Results: Of the top 28 genes that discriminated between the two cohorts, 21 were up-regulatedin the CD40 positive cohort, and coded for proteins involved in cell-to-cell and cell-to matrix interactions, e.g collagens (type VI alpha 1 and 2), proteoglycans (lumican, biglycan, versican), integrin alpha V, and for proteolysis (matrix metallopeptidase-2, uPAR, proteasome beta type 5).

Conclusions: The extracellular matrix provides a physical framework for cellular attachment and facilitates the regulation of cell proliferation, migration, and differentiation. CD40-expressing DLBCLs are characterized by an enhanced expression of genes encoding key components of the tumour stroma. The role of proteoglycans in lymphoma biology is largely unknown, and we are presently performing immunohistochemical studies for core proteins and chondroitin sulphate chains, the results of which will be presented at the conference.

191 HYPOXIA INDUCIBLE FACTOR (HIF)-1 AND -2 AND THE THIOREDOXIN FAMILY ARE ACTIVATED IN NON-HODGKIN'S LYMPHOMA (NHL): POTENTIAL PROGNOSTIC AND THERAPEUTIC IMPLICATIONS

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Introduction: HIFs are a family of heterodimeric transcription factors that activate multiple oncogenic signaling pathways including angiogenesis. The thioredoxins (TRXs), thioredoxin-1 (Trx1) and thioredoxin reductases-1 and -2 (TrxR1 and TrxR2), regulate the redox state and promote HIF. Little is known about HIF or the TRXs in NHL.

Methods: We examined HIF and TRX protein expression in 5 NHL cell lines by immunoblotting and studied HIF through a 90 patient (pt) tissue microarray (TMA).

Results: SUDHL4 and Raji cell lines demonstrated evidence of normoxic HIF-2 stabilization that was not seen in normal lymphocytes, while a small amount of normoxic HIF-1 stabilization was seen. We found increased TrxR1 expression in all cell lines, while only Namalwa, HF1 and SUDHL4 showed Trx1 and TrxR2 activation. Different levels of HIF expression were seen among diffuse large B-cell lymphoma (DLBCL) vs follicular lymphoma (FL) TMA cases, including 54% of DLBCL cases that showed moderate/high HIF-1 expression vs 20% of FL samples (p=0.001). 44% of DLBCL vs 11% of FL had moderate/high expression of HIF-1 and HIF-2 (p=0.0017), while 27% FL and 25% of DLBCL samples had no expression of HIF-1 or HIF-2. The 2-year event-free survival (EFS) was 43% and overall survival (OS) 65% for DLBCL pts with high expression of HIF-1 and HIF-2 vs 67% EFS and 76% OS without high expression (EFS p=0.09, OS p=0.34). Gene expression profiling of the tissue is underway and those data will be available at the meeting.

Conclusion: These data demonstrate that HIF and the TRXs are abnormally activated in NHL. Further studies are necessary to determine whether HIF and/or the TRXs promote NHL growth or progression, and to define the molecular interactions that may mediate this association. In addition, anti-HIF agents should be examined in NHL and study of the prognostic influence of HIF and the TRXs in larger pt cohorts is warranted.

192 SERUM-SOLUBLE TUMOR NECROSIS FACTOR RECEPTOR 2 (STNF-R2) LEVEL DETERMINES CLINICAL OUTCOME IN PATIENTS WITH DIFFUSE LARGE B CELL LYMPHOMA

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Introduction: Diffuse large B cell lymphoma (DLBCL) is a heterogeneous entity, with patients exhibiting a wide range of outcomes. The introduction of rituximab to CHOP (R-CHOP) has significantly altered improvement in survival. This raises concern regarding the utility of previously identified prognostic factors. In addition, some investigators have suggested that serum levels of cytokines and their soluble receptors might reflect tumor growth and host tumor responses. We reported before that Serum-soluble tumor necrosis factor receptors (sTNF-Rs), especially sTNF-R2, were strong prognostic factors in aggressive lymphoma patients who received CHOP without Rituximab (Eur J Haematol 2006:77:217-225). Tumor necrosis factor (TNF) is one of the earliest cytokines to be produced in inflammatory processes, thus plays a key role in initiating cytokine cascades. Serum sTNF-Rs levels rise in patients with some malignancies including malignant lymphoma.

Purpose: Whether sTNFR2 is a useful prognostic factor or not, we again examined sTNF-R2 level in patients with DLBCL treated with R-CHOP.

Methods: Untreated 83 consecutive patients (47 males, 36 females) with DLBCL were prospectively enrolled in this study between 2002 and 2006. The patients were treated with 6-8 cycles of R-CHOP regimens.

Results: 5-years Overall survival (OS) and progression free survival (PFS) rates of all patients were 66% and 64 %. High serum sTNF-R2 level was associated with some poor prognostic factors and low complete remission rate. Patients with high sTNF-R2 (20 ng/ml and over) at onset had significantly lower survival rates (3-year: 38%, 30%) than those with low sTNF-R2 (under 20 ng/ml) (91%, 87%), respectively ($p<0.0001$). Multivariate analysis employing sTNF-R2 and some conventional prognostic factors demonstrated that sTNF-R2 and PS were significant prognostic factors for poor OS ($p<0.01$; odds ratio 4.8, $p<0.05$; odds ratio 3.3) and for PFS ($p<0.05$; odds ratio 2.8, $p<0.005$; odds ratio 4.3) and respectively.

Conclusions: The results suggest that a high serum sTNF-R2 level predicts a poor prognosis in DLBCL and may be a useful biomarker for selecting appropriate treatment.

193 DELETIONS OF THE SHORT ARM OF CHROMOSOME 3 ARE RECURRENT ABNORMALITIES IN BURKITT'S LYMPHOMA

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Introduction: Deletions of the short arm of chromosome 3 have been reported in diffuse large B-cell lymphomas and various solid tumours. However, the incidence of 3p deletions in Burkitt's lymphomas (BL) has not been investigated so far.

Material and Methods: We herein report the molecular cytogenetic analyses on metaphases of 45 Burkitt's lymphoma cell lines and 1 BL patient with a cytogenetically determined 3p deletion using multicolor fluorescence in situ hybridization (mFISH) and FISH. We applied 25 overlapping bacterial artificial chromosome (BAC) probes spanning the whole short arm of chromosome 3, a DNA probe hybridizing to the alphoid repetitive DNA of the centromere of chromosome 3, and a probe hybridizing to the subtelomeric region of 3p.

Results: Deletions of 3p were found in 22% of the cases (9 BL cell lines and, as expected, in the BL patient) and were heterozygous in all cases. Five cases revealed interstitial 3p deletions that were not identified by mFISH analyses in 3 of the cases. The remaining 5 cases showed terminal deletions of 3p with centromeric breakpoints in 3p11 (3 cases) and in 3p14.3 (2 cases). We could further delineate a minimal deleted region of 3p based on the data from 9 of the 10 cases. This minimal deleted region on chromosome 3 was assigned to a 1,75 Mbp region in 3p21.1 and encompassed 26 annotated genes.

Conclusions: Our results revealed for the first time that deletions of the chromosome 3p arm occur recurrently in Burkitt's lymphomas and include a minimal deleted region in 3p21.1. Whether this minimal deleted region contains genes that are important in the pathogenesis of Burkitt's lymphomas remains to be determined.

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194 MGMT IN PRIMARY NODAL DIFFUSE LARGE B-CELLS LYMPHOMAS: SIGNIFICANCE OF IMMUNOHISTOCHEMICAL EXPRESSION AND METHYLATION STATUS

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Background: Loss of O^6-methylguanine-DNA-methyltransferase (MGMT) expression and presence of MGMT promoter methylation have been both proposed as favourable prognostic markers in diffuse large B-cell lymphomas (DLBCLs). However, there are very few studies which evaluate the relationship between the lack of immunoreactivity (IR) for MGMT and the methylation status of its promoter.

Materials and Methods: We studied 74 patients with primary nodal DLBCL, all treated with cyclophosphamide-containing regimens and with available follow-up information. MGMT-IR was detected using a specific monoclonal antibody. Cases showing less than 15% of IR neoplastic cells were considered as negative. The metilation status of MGMT promoter was analyzed in a subset of cases using a quantitative method based on Real Time methylation-specific PCR. For each sample we determined a methylation index (MI) and we considered cases with MI ≥20 as methylated.

Results: 28 out of 74 cases (38%) were negative for MGMT IIC expression, and all of them were studied for MGMT promoter metilation. We also analyzed the metilation status of 20 cases Immunoreactive for MGMT. All but 1 of the MGMT IR cases were unmethylated, while, only 52% of MGMGT negative cases showed MGMT promoter metilation. In addition, the survival analysis showed significantly longer overall survival in DLBCLs with MGMT promoter metilation compared with unmetilated cases, while the difference was not statistically significant when the IR and non-IR cases were compared.

Conclusions: These data suggest that the MGMT promoter metilation status, and not the loss of protein expression, is a favourable prognostic factor in primary nodal DLBCLs treated with cyclophosphamide-containing regimens. Immunohistochemistry seems to be an useful tool to identify unmethylated cases, while a methylation analysis should be performed when there is no or low expression of MGMT. The concomitant absence of protein expression and ptomoter methylation suggest allelic loss that will be investigated using FISH approach with bac probes of MGMT region.

195 DIFFERENTIAL DISREGULATION OF THE DLEU1 SIGNALING NETWORK IN BURKITT (BL) VS DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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Introduction: Deletions of 13q have been associated with a significant decrease in event-free survival (EFS) in children with BL treated on the international FAB/LMB 96 study. DLEU1 is a gene located on 13q and was identified within the Burkitt classifier genes by Dave/Staudt et al. NEJM, 2006.DLEU1-interactive proteins include E3 ubiquitin-protein ligase (UBR1), RASSF1A, Tubulin beta-2C (TUBB2C), ADP-ribosylation factor-like protein 8B (ARL8B), tumor antigen p53, and histone-lysine N-methyltransferase (SETDB1), which regulate G2/M cell cycle and lead to apoptosis.

Methods: We sought to compare the expression levels among these genes in BL vs DLBCL by microarray using Affymetrix U133A-2 and real-time RT-PCR.Twelve BL (10 patient samples and 2 cell lines, Raji and Ramos) and 3 DLBCL (1 patient sample and 2 cell lines, Pfeiffer and DB) were examined. In qRT-PCR, primers for UBR1 were CGGTGCCAGAACAGTCTGTATCCACG and AGAATGCAGATGCTCTTGCTCA (junction exon/exon 32/33), TUBB2C: CGTGAAGCATCTCCGAGCAGTTCAG and CCCGTGTACCAGTGCAGGAAG (exon 4), RASSF1A: CGGAACTCATCATCCAACAGCTTCG and AAGTTCTTGGTGGTGGATGACC (junction exon/exon 4/5).GAPDH was used as the house keeping gene. One way ANOVA and Welch Test were conducted for statistical analysis.

Results: BL expressed significantly higher levels of UBR1 (3.14±0.50F, $p<0.003$), TUBB2C (1.65±0.26F, $p<0.040$), RASSF1A (∞ F), and ERG (6.29±1.61F, $p<0.098$). No significant differences in gene expression were found in ARL8B (1.03±0.17F, $p<0.888$), p53 (1.46±0.52F, $p<0.411$), and SETDB1 (1.45±0.29F, $p<0.166$). qRT-PCR validated higher gene expression levels of UBR1 (4.70±0.81F, $p<0.0005$), TUBB2C (3.24±0.73F, $p<0.008$), and RASSF1A (2.52±0.50F, $p<0.039$) in BL than in DLBCL.

Conclusions: Taken together, DLEU1-network proteins are expressed differentially in BL compared with DLBCL, suggesting c-Myc promotes lymphoma transformation through different mechanisms in BL and DLBCL and DLEU1 may act as a tumor suppressor gate in c-myc-activated BL lymphomagenesis.

196 INCIDENCE OF BLIMP1 MUTATIONS AND THEIR ASSOCIATION WITH SURVIVAL IN 280 PATIENTS WITH DE NOVO DIFFUSE LARGE B CELL LYMPHOMA (DLBCL).

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Background: BLIMP1 (PRDM1) is a transcriptional repressor that allows germinal center B cells to undergo plasmacytic differentiation. BLIMP1 expression is high in the activated B cell-like (ABC) subtype of DLBCL and may function as a tumor suppressor.We assessed the incidence of BLIMP1 mutations and their association with survival (OS) in DLBCL pts treated with CHOP-R.

Methods: We PCR amplified and bi-directionally sequenced BLIMP1 exons using DNA from 280 DLBCL specimens collected at the BCCA after March 01 2001. Cell of origin (COO) was determined by gene expression profiling using Affymetrix U133-2Plus arrays on a subset of 76 pts. Mutations and single nucleotide polymorphisms (SNPs) in BLIMP1 were correlated with COO and OS.

Results: 280 pts had successful sequences for SNP analysis and 245 patients had successful sequences in all exons for mutation analysis.The clinical characteristics were: median age 64 y; male sex 40%; IPI 0-1 40%; 2-3 43%; 4-5 18%. 35% of pts progressed and died following CHOP-R over a median follow-up time of 3 y.37 different mutations were detected in 35 pts; 23 of these were exonic and 18 resulted in amino acid changes. In contrast to previous reports, 52% of exonic mutations occurred in exons 4 and 5 and were not exclusively confined to the NH2 domain, 89% were heterozygous and 13% predicted a severely truncated polypeptide. At the time of this analysis, COO was available in 76 patients (41 ABC subtype). Exonic BLIMP1 mutations were confined to the ABC subtype. There was no association between BLIMP1 mutations or SNPs with OS. However, when analysis was confined to the ABC subtype, BLIMP1 mutants trended towards an inferior OS.

Conclusions: The incidence of BLIMP1 mutations in 280 patients with de novo DLBCL was low (10%). Preliminary analysis suggests that mutations are confined to the ABC subtype supporting the hypothesis that BLIMP1 is important in the pathogenesis of this type of DLBCL. Survival analysis of BLIMP1 mutants within the ABC subtype and gene expression of Blimp1 targets including p53 (in mutated cases) will be presented.

197 EXPRESSION OF THE ETS-1 PROTO-ONCOGENE IN DIFFUSE LARGE B CELL LYMPHOMA: ROLE AS A PROGNOSTIC FACTOR

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Introduction: The Ets-1 transcription factor is believed to play a role in controlling the expression of the number of genes involved in extracellular matrix remodeling. It might play a role in the regulation of physiologic process such as cell proliferation and differentiation and also is associated with angiogenesis, cell migration, and tumor invasion. Therefore, we investigated, by immunochemistry, the expression of Ets-1, in diffuse large B cell lymphoma (DLBL) in order to demonstrate a correlation between the expressions of this gene and other prognostic factors.

Material and Method: We examined paraffin embedded tissue specimens of 73 patients with DLBCL by immunochemistochemical staining with Ets-1 antibody.

Result: Median age was 59 years and median survival was 53.77 months (95% CI: 40.94-66.59). Majority of specimens showed weak to moderate expression of Ets-1. Those patients who had lower Ets-1 showed better outcome in terms of survival. There was no statistical correlation between IPI index and Ets-1 expression extent. Ets-1 positivity was found to correlate with the duration of overall survival.

Conclusion: These findings suggest that Ets-1 is variably over-expressed in DLBCL tissues and it can be an independent prognostic factor in DLBCL.

198 DUAL TRANSLOCATIONS INVOLVING REARRANGEMENT OF *CMYC*ARE ASSOCIATED WITH A POOR PROGNOSIS IN RITUXIMAB TREATED DIFFUSE LARGE B-CELL LYMPHOMA PATIENTS

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Introduction: Rearrangement of *cMYC* is the defining cytogenetic abnormality of Burkitt lymphoma, however it is also demonstrated in diffuse large B-cell lymphoma (DLBCL) - usually in the context of a complex karyotype. It has been suggested that addition of Rituximab to CHOP chemotherapy may reduce the prognostic impact of some biological markers. The aim of the study was to determine whether the presence of dual translocations (particularly those involving cMYC) retains prognostic impact in the era of CHOP-R.

Methods: We have investigated 300 previously untreated DLBCL patients diagnosed between January 2004 to September 2006, using an extended panel of immunohistochemistry and interphase FISH for *cMYC*, *BCL6* and t(14;18)/*BCL2* rearrangements. Full data were available in 238 (median age 71 (range 23-96)). Patients were treated with CHOP-R and followed-up for a maximum of 3.9 years. Overall survival (OS) at 3-years was 49% (95% CI 42%, 56%). Patients with evidence of an underlying follicular lymphoma were excluded.

Results: In contrast to our previous data in CHOP treated DLBCL, neither the presence of *BCL2* or *BCL6* rearrangements nor expression of FOXP1 or germinal centre phenotype appeared to retain prognostic significance in univariate analysis in CHOP-R

treated patients. However, 26 (11%) patients had a t(14;18) and *cMYC* rearrangement, 10 (4%) were *BCL6* and *cMYC* rearranged, 16 (7%) were t(14;18) and *BCL6* rearranged and of these 7 had all 3 abnormalities. OS was significantly worse for patients with 2 or more rearrangements where *cMYC* was involved. The probability of survival at 2 years was 0.4 in the *cMYC* dual rearrangement group versus 0.6 for all others (log rank test, p=0.01).

Conclusions: The data is consistent with loss of prognostic impact of a number of biological prognostic markers in DLBCL patients treated with CHOP-R. A significant proportion of patients have two or more gene rearrangements, and overall survival was significantly inferior in the 12% of patients where the dual rearrangement included *cMYC*.

199 ASSOCIATION OF SERUM VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) A AND C WITH PROGNOSIS IN ADVANCED DIFFUSSE LARGE B CELL LYMPHOMA (DLBCL) TREATED WITH R-CHOP: A PROSPECTIVE STUDY

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Background: Restrospective studies have suggested that high pre-treatment VEGF-A level is associated with poor outcome in non-Hodgkin's lymphoma treated in the pre-rituximab era. The current study examined the prognostic significance of pre-treatment serum VEGF-A and VEGF-C levels in DLBCL patients (pts) treated with R-CHOP.

Material and methods: Between May 2002 and September 2004, serum VEGF-A and VEGF-C levels were prospectively analyzed in 86 pts with DLBCL. Serum VEGF-A and VEGF-C levels were assessed by enzyme-linked inmunosorbent assay before the first R-CHOP cycle.

Results: The median serum level was 641 pg/ml (range, 9-2790) for VEGF-A and 4843 pg/ml (range, 3671-5755) for VEGF-C. There were no correlations between VEGF-A or C levels and known clinical prognostic factors (IPI, LDH, performance status, stage or number of extranodal areas), except for VEGF-C and bulky disease (≥ 7 cm). Pts with bulky disease had a significant lower VEGF-C level (median 3950 pg/ml vs 5629 pg/ml; p<0,01). With a median follow-up of 48 months, 4 year-overall survival (OS) and progression free survival (PFS) were 75% and 60% respectively. OS and PFS were not different for pts with VEGF-A or VEGF-C levels above o below the median.

	VEFG-A <641 pg/ml	VEGF-A >641 pg/ml	p	VEGF-C <4843 pg/ml	VEGF-C >4843 pg/ml	p
4 y-PFS	55%	67%	<0,4	51%	68%	<0,08
4 y-OS	83%	70%	<0,2	71%	78%	<0,4

A significant 4 year OS (95% vs 67%, p<0,02) and PFS (80% vs 53%, p<0,04) advantage was observed in pts with pre-treatment VEGF-C levels above the third quartile.

Conclusion: In DLBCL pts treated with R-CHOP high pre-treatment level of VEGF-A or C is not associated with a worse outcome.

200 INCREASED BONE MARROW ANGIOGENESIS IN NON–HODGKIN'S LYMPHOMA

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Background: Whereas most studies report increased microvessel density (MVD) in lymph nodes of non–Hodgkin's lymphoma (NHL) patients, it is unclear if angiogenesis is increased also in their bone marrows and whether it changes upon therapy.

Material and methods: We evaluated bone marrow MVD using microscopic evaluation of CD34–labelled specimens from 48 consecutive patients with NHL. We also measured the plasma levels of six proangiogenic factors using multiplex flowcytometry. Finally, the mRNA expression of 37 angiogenesis–related genes in blood mononuclear cells was determined with quantitative RT–PCR.

Results: We found that patients had higher MVD in their bone marrows, higher plasma levels of VEGF, angiogenin, TNFα, and IL–6; higher mRNA expression of VEGF, VEGFB, tumour protein 53 (TP53), and hypoxia inducible factor 1α; and lower mRNA expression of notch homolog 4 (NOTCH4) than healthy controls. Patients with Ann Arbor stage IV disease had higher mRNA expression of VEGFB, angiopoietin 2 (ANGPT2) and TP53, and lower expression of chemokine ligand 2 (CCL2), NOTCH4 and tissue factor pathway inhibitor (TFPI) than those with lower stage disease. Patients who did not obtain complete remission (non–CR) had higher mRNA expression of ANGPT2 and lower expression of CCL2 and NOTCH4 before cancer therapy. After cancer therapy, non–CR was associated with higher mRNA expression of VEGF, angiogenin, FGF2 and IL–6; and lower expression of NOTCH4, and TFPI. No difference was observed when comparing the 21 patients with indolent disease with the 27 with aggressive disease for any of the parameters; neither bone marrow MVD, plasma levels nor mRNA expression.

Conclusion: Angiogenesis seems to be increased in the bone marrow of patients with NHL. This may be related to higher levels of proangiogenic cytokines and differential expression of angiogenesis–related genes.

201 CLINICAL FEATURES AND PROGNOSIS OF DIFFUSE LARGE B-CELL LYMPHOMA WITH T(14;18) AND 8Q24 TRANSLOCATIONS

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Introduction: About 25-30% of diffuse large B-cell lymphomas (DLBCLs) have the t(14;18)(q32;q21) translocation, and about 5-10% of DLBCLs have 8q24 translocation. However, DLBCL having both t(14;18) and 8q24 is rare. We evaluated the clinical characteristics and prognoses of patients with DLBCL carrying both t(14;18) and 8q24 translocations.

Patients and Methods: A total of 1,864 consecutive patients with non-Hodgkin's lymphoma were treated in the Adult Lymphoma Treatment Study Group (ALTSG) from 1998 to 2007. Chromosomal data were available in 643 of the 1,114 patients with DLBCL. Seventeen cases of DLBCL with the dual translocation were identified. Patients were treated with the cyclophosphamide, vincristine, bleomycin, etoposide, doxorubicin, and prednisolone (CyclOBEAP) regimen or CHOP regimen. Rituximab was administered to the 5 patients diagnosed after 2005.

Results: The dual translocation was seen in 17 (4%) of the 394 patients with DLBCL. There were 9 males and 8 females, with a median age of 61 years (range, 29-79 years). The dual translocation was observed significantly more frequently among patients with high LDH level, among patients with B symptoms, and among patients with an advanced stage. Bone marrow infiltration was found in 16 of the 17 patients. Immunophenotyping analysis (CD20, CD5, CD10, BCL-2, BCL-6, MUM-I, KI-67) showed DLBCL of the germinal center type. Ki-67 staining ranged from 80-90%. Complete response was achieved in 47%. The 5-year overall survival was 65% among the all patients with DLBCL, 44% among the patients with 8q24 translocation, and 0% among the patients with t(14;18)+8q24 translocation. The dual translocation group showed significantly poorer prognosis than the other translocation. Even when rituximab combination chemotherapy was administered, prognostic improvement was not seen.

Conclusions: DLBCL patients with concurrent t(14;18) and 8q24 translocations have a very poor prognosis. The poor outcome of these patients appears to be independent of other prognostic indicators and is thought to be related to clonal evolution and the synergy of growth promotion by c-MYC and the antiapoptotic effect of BCL-2 gene dysregulation.

202 THE COMBINED EVALUATION OF INTERIM CONTRAST-ENHANCED COMPUTERIZED TOMOGRAPHY (CT) AND FDG-PET/CT PREDICTS THE CLINICAL OUTCOMES AND MAY IMPACT ON THE THERAPEUTIC PLANS IN PATIENTS WITH AGGRESSIVE NON-HODGKIN'S LYMPHOMA

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We investigated the concomitant interim response of patients with aggressive non-Hodgkin's lymphoma (NHL) using conventional computerized tomography (CT) and FDG-PET/CT. This may help predict the clinical outcomes and may provide the differentiate potentials to make a risk-adapted therapeutic plans in individual patients.

Patients and Methods: Newly diagnosed 102 patients with aggressive NHL were enrolled between Aug. 2004 and Aug. 2007. Both the CT and PET/CT were serially performed at the time of diagnosis and after the 3rd or 4th chemotherapy. The patients

were categorized into four different responsive groups according to the interim PET/CT and CT: 1) Complete metabolic response (CMR)-complete response unconfirmed (CRu), 2) CMR-partial response (PR), 3) partial metabolic response (PMR)-CRu, and 4) PMR-PR.

Results: The median age was 57 years, with 41.2% patients aged higher than 60 years. Fifty-three patients with CMR-CRu, 21 patients with CMR-PR, 6 patients with PMR-CRu, and 20 patients with PMR-PR were distributed. We found a significant difference in relapse rates between PET-positive (58.3%) and PET-negative (8.1%). In particular, 70% of patients with PMR-PR experienced a relapse during or after the completion of chemotherapy. We also found significant differences between patients with PMR-PR (31.1% and 29.2%) and CMR-CRu (86.4% and 86.0%) for 2-year overall survival (OS) and event-free survival (EFS), respectively. In multivariate analysis, high IPI (≥3) at diagnosis and PMR-PR in interim PET/CT and CT were independent prognostic significances for OS with a hazard ratio (HR) of 2.89 (1.15 – 7.23) and 3.22 (1.16 – 8.92), respectively. Moreover, bulky (>10 cm) and PMR-PR showed significant associations for EFS with a HR of 3.73 (1.49 – 9.33) and 4.35 (1.79 – 10.56), respectively.

Conclusion: The combined evaluation of interim PET/CT and CT was found to be a significant predictor of disease progression, OS and EFS.

203 NEGATIVE PET/CT POST-INDUCTION IS MORE SIGNIFICANT THAN INTERIM POSITIVE PET/CT IN PREDICTING PROGRESSION-FREE AND OVERALL SURVIVAL IN AGGRESSIVE NON-HODGKINS LYMPHOMA: REVIEW OF LITERATURE

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Introduction/Background: Investigators reported early PET/CT positivity (+) to be a strong predictor of progression free (PFS) & overall survival (OS). However, recently investigators have proposed PET/CT negativity (-) post-induction may be a more significant predictor of PFS & OS than the International Prognostic Factors Index (IPI) &/or other prognostic factors. The effect of rituximab on altering the value of PET results has also not been previously addressed. We evaluated PET/CT post-induction as a predictor of PFS & OS in the treatment of NHL through review of literature.

Material & Methods: We evaluated literature in PubMed with PET/CT, NHL, staging, response, IPI & rituximab. This generated 15 articles discussing current practices of interim & post induction PET/CT as predictors of PFS & OS with R-CHOP, histology and IPI.

Results: Most studies included pts with various histologies, differing IPI scores & treatment. In three studies, PET/CT negativity post-induction was an important predictor of PFS & OS for patients with aggressive NHL. Mikhaeel & colleagues found that interim PET/CT results were good predictors of complete response (CR), Event Free Survival (EFS) & OS in a study of 121 pts. Haioun & colleagues evaluated 90 pts with aggressive NHL and reported pts who were PET/CT (+) early on converted to PET/CT (-) post-induction. In the third study, Pregno & colleagues reported early interim PET/CT was useful in determining chemo-sensitivity & initial response but not in determining PFS &OS. All of these pts had received R-CHOP therapy. Post-induction PET/CT (-) could predict PFS & OS; however, pts with early interim PET/CT (+) could still achieve a CR with further therapy.

Conclusions: Investigators have reported that PET/CT negativity early in therapy is an important predictor of PFS & OS in aggressive NHL. IPI, histology & type of therapy also need to be considered in response assessment. We conclude that pts who are in early interim CR by PET/CT have excellent PFS and OS, however, those pts in CR post-induction therapy can have an even more significant PFS & OS.

204 PROSPECTIVE EVALUATION ON THE VALUE OF FDG-PET/CT FOR RESPONSE ASSESSMENT IN DLBCL AFTER 1 WEEK OF R-CHOP

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Introduction: Risk-adapted treatment strategies based on pre-treatment prognostic factors showed that intensification of therapy improves the cure rate in high-risk patients with diffuse large B-cell lymphoma (DLBCL). However, intensified approaches are associated with an increased toxicity, which may be acceptable in high-risk patients, but is more controversial for the large intermediate-risk patients who have a substantial chance to be cured with less toxic treatments. In these patients, the individual sensitivity of the tumor to the administered treatment is probably more important than the extent of disease at diagnosis. Chemosensitivity can be measured with FDG-PET and a decrease of FDG-uptake in DLBCL was documented already at 7 days after treatment. To investigate whether PET after one week can predict outcome, we conducted a prospective study where FDG-uptake was quantified exactly 7 days after therapy.

Patients and methods: Twenty-nine patients with DLBCL underwent FDG-PET exactly one week after the first administration of R-CHOP. PET-results were qualitatively and semi-quantitatively analysed (standardized uptake value, SUV) and compared with outcome (median follow-up 20 mnths). Optimal cut-off values were defined with ROC analysis.

Results: Twelve out of 29 patients obtained a complete resolution of FDG-uptake at day 7 after therapy, and non of these patients relapsed after a median follow-up of 19 months. Seventeen patients had significant FDG-uptake on early PET and 13 of them were disease free after a median follow-up of 20 months. An optimal cut-off value of 61% decrease in SUV_{mean} yielded a sensitivity of 100% but a specificity of only 58%.

Conclusions: This interim-analysis shows that a negative PET after one week of therapy is highly predictive for a good prognosis. However, in patients who still have significant FDG-uptake, a high variability was seen with a limited specificity for the prediction of relapse. This series does therefore not justify the intensification of therapy in patients with significant FDG-uptake after one week of treatment, even if there is only a minor response on early PET.

205 R-IPI AS A PREDICTOR OF SURVIVAL IN PATIENTS WITH DIFFUSE LARGE CELL B-CELL LYMPHOMA (DLBCL) TREATED WITH R-CHOP CHEMOTHERAPY

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Introduction/Background: The revised International Prognostic Index (R-IPI) has recently been proposed by *Sehn et al.* to more accurately estimate survival in patients with DLBCL, treated with immunochemotherapy compared to the IPI. We performed a retrospective analysis of patients treated at our institution to determine if the R-IPI more accurately estimated survival in our cohort and therefore validate the R-IPI.

Materials and Methods: A retrospective review of patients with DLBCL who were treated with R-CHOP chemotherapy at Mayo Clinic between January 2001 and December 2004 was done. Patients were age ≥ 16 years of age, had newly diagnosed biopsy proven DLBCL, and were treated with curative intent.

Results: Ninety patients were identified and clinical characteristics include a median age at diagnosis of 65 (range, 22-87 years) and 47 patients (52%) were male. Thirty three (36%), 25 (28%), 6 (7%) and 26 (29%) patients has stage I, II, III, and IV disease, respectively. Forty eight patients had low IPI, 22 had low intermediate, 13 high intermediate and 7 high IPI. Patients were categorized by the R-IPI (0 IPI risk factors: very good (VG); 1-2: Good (G); 3-5: Poor (P), respectively) and then analyzed. Nineteen patients (21%) had an R-IPI of very good (VG), 52 patients (58%) Good (G), and 19 patients (21%) Poor (P). With a median follow-up of 50 months, 4 year progression free survival (PFS) grouping patients with the IPI was 88%, 62%, 52%, and 28% in low, low intermediate, high intermediate, and high risk groups and with the R-IPI was 94, 75, and 45% respectively ($p<0.001$). Four year overall survival (OS) with the IPI was 94%, 76%, 61%, and 53%, and with the R-IPI was 94, 86, and 56%, respectively ($p=0.001$).

Conclusions: The R-IPI as applied to our cohort identified three groups with statistically different 4 year PFS and OS, similar to those previously reported by the British Columbia Cancer Agency. The R-IPI thus divides patients into 3 more distinct prognostic groups than the IPI. Future studies should use the R-IPI to stratify patients into very good, good and poor risk categories.

206 MULTI-CENTER STUDY OF DOSE-ADJUSTED EPOCH-R IN UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA-CALGB50103

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Introduction: DA-EPOCH-R+G-CSF was rationally designed based on schedule optimization and pharmacodynamic dosing to overcome adverse effects of tumor proliferation and adjust for patient drug clearance. An NCI study in 72 untreated DLBCL patients shows a PFS and OS of 79% and 80%, respectively, at the median follow-up of 4.5 years with no progressions beyond 2 years following therapy. PFS is 91%, 67% and 47% in IPI subgroups with 0-2, 3, and 4-5 risk factors, respectively, at 4.5 years (JCO submitted).

Methods: CALGB cooperative group phase II confirmatory study in similar patients at 18 centers. Eligibility-untreated de novo CD20+ DLBCL; ≥ 18 years; stage II-IV; and ECOG PS 0-2. Patients received 6-8 treatment cycles, based on response, and no radiation.

Results: Of 78 patients, 6 were ineligible (2 did not start treatment; 4 incorrect histology). Characteristics-median age 59 (range: 23-83) years, and IPI risk factors 0-2 in 60% and 3-5 in 40% of patients. The pharmacodynamic endpoint of grade 4 neutropenia occurred in 96% of patients. Febrile neutropenia occurred in 36% of patients with grade 4 anemia and thrombocytopenia in 10% and 17%, respectively. Significant gastrointestinal, thrombotic or neurological toxicities were infrequent, there were no cardiac failures and there was one treatment associated death from CNS hemorrhage. 92% of patients completed at least 6 cycles. Response was 53 (74%) CR, 17 (23%) PR, and 2 (3%) NR due to one patient off study after 1 cycle and 1 treatment-related death. At the median follow-up of 3.8 years, and with a minimum follow-up of 2.5 years for patients in remission, the PFS, EFS and OS are 80%, 74% and 84%, respectively, and there are no progressions beyond 2 years. Among IPI subgroups with 0-2, 3, and 4-5 risk factors, PFS is 93%, 72% and 54%, respectively, at 3.8 years.

Conclusion: This study indicates that DA-EPOCH-R can be successfully administered in a cooperative group setting and its encouraging outcome is unlikely due to patient selection. A CALGB randomized phase III study of DA-EPOCH-R versus R-CHOP with microarray tumor analysis is ongoing.

207 LONG-TERM RESULTS FROM THE U.S. INTERGROUP TRIAL OF RITUXIMAB-CHOP VS CHOP FOLLOWED BY MAINTENANCE VS OBSERVATION IN DLBCL

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Background: The E4494 Trial demonstrated a signifcant advantage for CHOP + rituximab induction when reported in 2006 with a median follow-up of 3.5 years. At this time, we report a median 7-year follow-up of the induction therapy.

Methods: 632 patients (pts), age 60 or older, with DLBCL were randomized to CHOP with rituximab (R-CHOP) administered Day -7, -3, and 2 days before cycles 3, 5, and 7, vs CHOP for a total of 6-8 cycles. Pts were stratified by the International Prognostic Factor Index (IPI) as 1 vs 2-4. 415 pts underwent the second randomization to rituximab 375 mg/M^2 weekly times 4, repeated every six months times 4 (MR) vs observation. Failure-free survival (FFS) and overall survival (OS) were estimated applying a weighted analysis to remove the influence of MR as previously reported (JCO 2006).

Results: The 7-year FFS was 42% (95% CI, 0.36,0.45) for R-CHOP and 34% (95% CI, 0.29,0.40), (p=0.004). The FFS in R-CHOP in low risk pts (IPI 0-2) was 53% (95% CI, 0.43, 0.65) VS 44% (95% CI, 0.35, 0.55) (p=0.063) and 36% (95% CI 0.29, 0.44) vs 28% (95% CI, 0.22, 0.36) in high risk IPI (3-5) subsets (p=0.025). The overall survival (OS) for R-CHOP was 52% and 47% for CHOP (p=0.12).

Conclusion: R-CHOP induction, as adminstered in the U.S. Intergroup trial, continues to demonstrate significantly superior FFS in patients age 60 and greater. Survival differences were not as great as the recent update from the GELA (ASCO 2007), and this appears to be related to better outcomes in the CHOP arm in the U.S. Intergroup study (47% vs 36%) as the 7-yr R-CHOP results are nearly identical (52% vs 53%).

208 RITUXIMAB FOR CD5-POSITIVE & CD5-NEGATIVE DIFFUSE LARGE B-CELL LYMPHOMA

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Background: Prognosis of diffuse large B-cell lymphoma (DLBCL) is markedly improving in recent years of rituximab era. Prognosis of *de novo* CD5-positive DLBCL has been reported poor, but the effect of rituximab for this type of lymphoma remains unclear.

Materials and methods: From April 1998 to October 2006, a total of 424 patients were diagnosed with DLBCL in the Yokohama City University and collaborating institutes. Of these, 157 were analyzed by flow-cytometry and received chemotherapy. Those treated with radiotherapy alone or only with supportive therapy were excluded from this study. Patients diagnosed in 2003 or later were treated with rituximab combined chemotherapy.

Results: There were 95 males and 62 females. The age ranged from 20 to 91 years old, and the median was 65 years. Nineteen patients were diagnosed to have *de novo* CD5-positive DLBCL (M:F=8:11), and the age ranged from 30 to 91 (median: 66) years old. Rituximab was added to the chemotherapy in 85 patients. Of these, 11 were positive for CD5 and 74 were negative. For patients treated without rituximab, overall survival (OS) of CD5-positive and –negative group were not different (5-year OS: 50% vs. 49%, p=0.72). However, for patients treated with rituximab containing chemotherapy, CD5-negative group showed better prognosis as compared with CD5-positive group (3-year OS: 84% vs. 59%, p=0.04). Prognosis of CD5-positive group did not improve after the introduction of rituximab.

Conclusion: Rituximab improves prognosis of CD5-negative DLBCL when combined with standard chemotherapy, but not for CD5-positive DLBCL. Further strategies are required to remedy the poor prognosis of CD5-positive DLBCL.

209 TREATMENT RESPONSE PREDICTOR USING ^{31}P MRS FOR CHOP AND R-CHOP THERAPY IN DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction: Our research has demonstrated in various forms of non-Hodgkin's lymphomas (NHL) that the sum of *phosphoethanolamine* plus *phosphocholine* [Etn-P+Cho-P] normalized by the total nucleotide triphosphates (NTP) in the tumor measured prior to treatment can predict treatment failure and drug-free survival while the power of these predictions increases when the parameter is combined with the international prognostic index (IPI), a clinical prognosis parameter for NHL. To make our results diagnosis- and treatment- specific, we selected patients with diffuse large B-cell lymphoma (DLBCL) treated with CHOP or similar treatments and divided these patients in those that did not receive rituximab (R-) and those that did (R+). Because rituximab has recently shown increased response rates and drug-free survival, we explored if this drug modified the predictive benefit of [Etn-P+Cho-P]/NTP.

Procedures & Patients: Tumor areas of 22 DLBCL patients were studied with *in vivo* 3D-localized phosphorus MR spectroscopy; 14 of them R- and eight R+.

Results: In both the R- and R+ groups the pre-treatment [Etn-P+Cho-P]/NTP showed significant differences between patients that responded completely to therapy (CR) and those that did not (NCR). The mean ± standard error for the CR and NCR cases for the R- group were 1.38±0.23 (n=9) and 2.35±0.19 (n=5) respectively (p<0.007) whereas for the R+ were 1.72±0.19 (n=4) and 2.58±0.19 (n=4) respectively (p<0.02). The Fisher test of the R- group using a threshold of 1.78 by ROC analysis also showed significance (p<0.03, sensitivity=0.67, specificity=1.00). The patients were divided into low, intermediate and high risk groups using the IPI and a threshold for the pre-treatment [Etn-P+Cho-P]/NTP generated by classifying correctly as many cases as possible. A significance of p<0.0002 and a sensitivity and specificity of 0.92 and 0.89 respectively were found in a Fisher test with only two misclassified cases. Using this IPI-dependent threshold, drug-free survival was analyzed using Kaplan-Meier and Tyrone-Ware procedures. A significant drug-free survival difference was found amongst the patients above and below the IPI-dependent threshold (p<0.0001).

Conclusion: The pre-treatment [Etn-P+Cho-P]/NTP ratio predicts long-term failure to treatment and drug-free survival in DLBCL patients treated with CHOP therapy. Despite of its therapeutic benefit, rituximab does not alter the predictive value of this parameter.

210 EXCELLENT LONG TERM SURVIVAL OF FRONT-LINE HIGH-DOSE CHEMOTHERAPY WITH RITUXIMAB (HDT) IN ADULTS WITH AGGRESSIVE LARGE B-CELL LYMPHOMA (DLBCL)

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Background: Superiority of HDT with autologous stem cell transplantation (ASCT) in the upfront treatment of poor-risk DLBCL remains an option for intermediate-high (IH) or high IPI young adults. We updated results of the prospective trial Goelams 074 to evaluate long-term efficacy and toxicity in 42 patients who underwent HDT with ASCT.

Methods: A prospective pilot trial was proposed to patients with DLBCL, with IH or high adjusted IPI, up to the age of 60 y.o. This program consisted of 2 courses of high-dose CHOP-like regimen with Rituximab, followed by a course of high-dose methotrexate with cytarabin. For patients who achieved at least a PR, ASCT started with a BEAM regimen.

Results: Between 04/2002 and 05/2003, 42 pts were included. Median age was 50 y.o (18–60 y.o), 23 had WHO PS 2, 41 had LDH level >N and 38 had stage III or IV disease. The age-adjusted IPI was IH in 23 and was high in 19 pts. The program was completed in 30 pts (71%): there were 3 toxic deaths, 8 treatment failure and 1 ASCT refusal. In an intention-to-treat analysis, the 5-year overall survival is 74% and event-free survival (event: death, relapse, severe toxicity) is 52%. Median survival is not reached. 10 patients (33%) relapsed after HDT but 4 were successfully re-treated and are in complete second response. With a median follow-up of 51 months, only 2 toxic events have occurred: 1 lung cancer and 1 cardiac dysfunction followed an anthracycline-based regimen (R-CHOP) for relapse. Both patients are alive in complete remission. No myelodysplasia has occurred.

Conclusion: First-line HDT with Rituximab offers very good results for young adults with IH or high adjusted IPI DBLCL with a 5-year OS of 74% and is currently being compared with classical CHOP-R regimen. Late toxicity is very acceptable.

211 THE R-MEGACHOP-ESHAP-BEAM STUDY FOR HIGH-RISK AGGRESSIVE B-CELL LYMPHOMAS: PATIENTS WITH EARLY PET NEGATIVITY HAVE EXCELLENT LYMPHOMA-FREE SURVIVAL

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Background: The Czech Lymphoma Study Group (CLSG) have treated 105 patients with DLBCL or grade 3 follicular lymphoma, aaIPI 2 or 3, with intensive R-MegaCHOP-ESHAP-BEAM regimen. This regimen uses 3 cycles of high-dose R-CHOP, followed by 3 cycles of R-ESHAP and BEAM with ASCT. The overall and progression-free survival (OS and PFS) was 76% and 74% in three years, however, 7 patients have suffered toxic death during treatment. If early PET could identify patients with good lymphoma-free survival (LFS), the treatment-related deaths might be prevented by reducing the treatment for these patients.

Methods: Early PET was defined as PET scan performed after 2nd or 3rd cycle of R-MegaCHOP. OS, PFS and LFS for PET positive and PET negative patients were compared with log-rank test. LFS was determined after excluding patients who suffered toxic death.

Results: Of 105 patients in the study, 51 had early PET (49%). Their median age was 39 years, 50% of them were men and 41% had aaIPI 3. Of these 51 patients, 35 patients were PET negative (69%), and 16 positive (31%). There was no difference in OS or PFS between PET negative and PET positive patients. However, as all three toxic deaths have occured in the early PET negative group, the 3-year LFS was significantly better for PET negative patients (98% v. 71%, p = 0,01). Of 16 early PET positive patients, 10 were scanned later during the course of treatment; 9 have achieved PET negativity and of them, only 2 had relapsed.

Conclusion: In high-risk patients treated with R-MegaCHOP induction, those who achieved PET negativity after 2nd or 3rd cycle had excellent LFS and some of them might be spared of toxic death by reduction of treatment. On the other hand, patients with positive early PET scan might still have good lymphoma-free survival after further intensive therapy with ASCT.

212 COMPREHENSIVE GERIATRIC ASSESSMENT-ADAPTED CHEMOTHERAPY IN ELDERLY PATIENTS (>70 YEARS) WITH DIFFUSE LARGE B-CELL NON-HODGKIN'S LYMPHOMA (DLBCL)

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Background: R-CHOP is the standard chemotherapy (CT) regimen for elderly patients (pts) with CD20+ DLBCL. However, many pts aged 70 years (yrs) or more are often unable to receive R-CHOP and the majority of them are excluded from clinical trials. Comprehensive geriatric assessment (CGA) has been demonstrated an useful instrument to predict the clinical outcome of elderly pts with cancer. Within the GOL (Gruppo Oncoematologico Linfomi) we started a phase II prospective study with the aim to evaluate feasibility and activity of a CGA-driven CT for elderly pts with DLBCL.

Material and methods: Pts with no comorbidity received CHOP/R-CHOP; in pts with mild cardiopathy epirubicin was used instead of doxorubicin (CEOP/R-CEOP); in pts with moderate/severe cardiopathy the use of anthracyclines was omitted (CVP/R-CVP); pts with diabetes didn't receive prednisone (CHO/CEO/R-CHO/R-CEO); pts with neuropathy received CHP/R-CHP/CEP/R-CEP. The dosage of CT was decided according to the CGA: pts with a good score of CGA (i.e. ADL=6 and IADL>6) received full doses of CT; pts with an intermediate score (ADL=5 and IADL>4) received 75% of the planned dose; pts with a poor score (ADL<5 and IADL<5) received 50% of the planned dose.

Results: One hundred pts have been treated. The median age was 75 yrs (range 70-89). Overall, 86% of pts received an anthracycline and 54% received rituximab plus CT. Toxicity was quite acceptable. Grade 3-4 neutropenia was observed in 30% of pts, mucositis in 12%, peripheral neuropathy in 9%. Four toxic deaths were observed. Overall, 81% ofpts achieved a complete remission, with a median follow-up of 33 months (range 1-77 months); 17% of them have relapsed. The 3 yr-OS, DFS, EFS are 71%, 80% and 58%, respectively.

Conclusions: Our results demonstrate that a CGA-driven approach is feasible and highly active in elderly pts with DLBCL. Moreover this strategy allows to offer a curative approach to all pts with aggressive NHL, avoiding to undertreat pts with a potentially cured disease.

213 PHASE III RANDOMIZED TRIAL COMPARING R-CHOP VS R-MINICEOP IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (B-DLCL) PROSPECTIVELY SELECTED BY A MULTIDIMENSIONAL EVALUATION SCALE

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In 2003 the IIL started a phase III study to compare R-CHOP vs R-miniCEOP regimens for the initial treatment of elderly patients with B-DLCL. The study was also aimed at assessing the usefullness of a Multidimensional Evaluation Scale (MES) to prospectively identify patients eligible to full doses chemotherapy. MES questionnaire included comorbidity, ADL, IADL and geriatric syndrome scales. Main inclusion criteria were age ≥ 65 years, stage II-IV, non-frail status based on MES rules. Eligible patients were randomized between 6 courses of R-CHOP-21 and R-miniCEOP-21 (vinblastine 5mg/sqm instead of vincristine; epidoxorubicin 50mg/sqm instead of doxorubicin). Study was closed on dec 2006 after enrollment of 288 patients: 236 patients were non frail at MES and were randomized; 2 patients were excluded (stage I disease; concomitant neoplasia). The clinical characteristics of the 234 randomized cases (R-CHOP: 114; R-mini-CEOP: 120) were median age 71 years, M/F 1.1, Stage III-IV 69%, > 1 ENS 27%, aaIPI 2-3 47%. CR rate was 74% and 65% of in the R-CHOP and R-miniCEOP arms, respectively (p=0.233). Toxicity was similar in the two arms. After a median follow-up of 18 months, 2-yrs EFS and OS were 52% and 70%, with no differences between study arms. Analysis of MES data did not identify any comorbid condition, or ADL, or IADL scores of prognostic relevance. Among 53 non randomized frail patients, curative treatment was planned in 28 cases; for these cases a worst outcome was observed compared to non-frail patients (2yr OS of 46% vs 70%; p=0.007). In conclusion MES represents a valid tool for identifying elderly patients with B-DLCL eligible to full doses chemotherapy and its use is recommended for future trials. The addition of Rituximab to a less intensive chemotherapy regimen (mini-CEOP) represent a good alternative to standard R-CHOP for the treatment of elderly patient with B-DLCL.

214 6 VERSUS 8 CYCLES OF R-CHOP-14 IN ELDERLY PATIENTS WITH DLBCL

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Background: While CHOP is widely accepted standard chemotherapy regimen of care for aggressive lymphomas, the optimal number of chemotherapy cycles for the treatment of aggressive lymphomas has not been determined.

Methods: In the RICOVER-60 trial, 1222 elderly pts. (61-80 years, stages I-IV) were randomized to receive 6 or 8 cycles of CHOP-14 with or without Rituximab (R) given on days 1, 15, 29, 43, 57, 71, 85, and 99. Radiotherapy was planned to sites of initial bulk/e-involvement.

Results: In a multivariate analysis adjusted for prognostic factors using 6xCHOP-14 without R as the reference, all intensified regimens improved EFS. Compared to 6xCHOP-14, PFS improved after 6xR-CHOP-14 and 8xR-CHOP, while OS improved only after 6xR-CHOP-14. Further analysis to identify subgroups taking benefit from 2 additional cycles has been performed. The outcome after 6 cycles was at least as good as 8 cycles, in any risk group according to IPI. Compared to pts. in CR after 4 cycles (n=261), pts. in PR after 4 cycles (n=459) had a significantly worse 3-year PFS (63% vs. 75%; p=.001) and OS (69% vs. 84%; p=0.001), while for pts. in CRu (n=276) this applied to PFS (68% vs. 76%; p=0.043), but not to OS (78% vs. 84%; p=0.125). Among pts. with mid-therapy CRu, the 3-year PFR receiving 6 cycles (6x-CHOP-14: 65%, 6xR-CHOP-14: 72%) and those receiving 8 cycles (8xCHOP-14: 63%; 8xR-CHOP-14: 71%) were not different (p=0.601 and p=0.815 without and with R, resp.). The same was true with respect to OS (6xCHOP-14: 82%; 8xCHOP-14: 70%; 6xR-CHOP-14: 80%; 8xR-CHOP-14: 80%; p=0.422 and p=0.759 without and with R, resp.), irrespective of additional radiotherapy or not.

Conclusion: Pts. in CR after 4 cycles of therapy have a better outcome than those in CRu and PR at mid-therapy, with no difference between pts. who received 6 and 8 cycles of (R-)CHOP-14. Response-adapted assignment of 8 cycles instead of 6 does not compensate for the worse prognosis of pts. achieving less than a CR after 4 cycles.
Supported by Dt. Krebshilfe

215 PEG-FILGRASTIM (PEG-F) ON DAY 4 OF (R-)CHOP-14 CHEMOTHERAPY IS SUPERIOR TO DAY 2 IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL-LYMPHOMA (DLBCL): RESULTS OF A RANDOMIZED TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN-LYMPHOMA STUDY GROUP (DSHNHL)

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Background: Application of peg-f is recommended on day 2 of chemotherapy, but later application has not been studied.

Objective: To compare the effects of peg-f given on day 4 instead of day 2 on the endpoints feasibility, leukocyte counts, rate of infections and therapy-associated deaths after CHOP-14 with and without rituximab (R).

Methods: Intention-to-treat-analysis of 109 elderly patients (median 69 years) with DLBCL receiving CHOP-14 or R-CHOP-14 randomized to peg-f on day 2 or day 4 (D4).

Results: Of 103 evaluable pats., 51 received peg-f on day 2 (D2) and 52 on day 4 (D4). D2 and D4 populations were well balanced for known risk factors, and there was no difference between pts. receiving CHOP-14 and R-CHOP-14 with respect to the above mentioned endpoints. Both D2 and D4 allowed for an excellent adherence to (R)-CHOP-14 protocol, with a median relative dose of myelosuppressive drugs of 98% (D2) and 99% (D4), respectively. Leukocytopenia <2000/mm^3 lasted for 3 (day 8 to 10) after D2 and 1 day (day 9) after D4. Grade 4 leukocytopenia (<1000/mm^3) occurred in 47% of all cycles after D2 and in 20.5% after D4 (p<0.001). Grade 30.118). There were 4 therapy-associated deaths (all infection-associated) in the D2 and 1 (none infection-associated) in the D4 group (p=0.205 for all and p=0.057 for infection-associated deaths).

Conclusions: Peg-f allows for excellent adherence of elderly patients to (R)-CHOP-14. Peg-f should be given on day 4 instead of day 2, because D4 results in less leukocytopenia, less infections and less therapy-associated deaths. An analysis whether the favourable end-high infectious profile of D4 application translated into better outcome will be presented.
Supported by Amgen

216 R-ESHAP AS SALVAGE THERAPY FOR PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA: INFLUENCE OF PRIOR EXPOSURE TO RITUXIMAB ON OUTCOME (A GEL-TAMO STUDY)

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Background: At present, the optimal second-line regimen for patients with relapsed or refractory diffuse large B-cell lymphoma (DLBCL) is unclear, and the benefit of the inclusion of rituximab (R) in salvage therapy for patients previously exposed to this agent is also unclear.

Patients and methods: We have retrospectively analysed 163 patients (pt) with DLBCL who received R-ESHAP as salvage therapy between May 2000 and July 2007. Median age was 54 years (19-70). The analysis was performed according to whether patients had (n=94, "R+" group) or had not (n=69, "R-" group) received R prior to R-ESHAP.

Results: Overall response (OR) rate to R-ESHAP was 73%, with 74 pt (45%) achieving complete response (CR) and 45 (28%) partial response (PR). Patients in the R+ group had lower CR (37% vs 56%, p=.015) and OR (67% vs 81%, p=.045) rates than patients in the R- group. However, in multivariate analysis, the single factors with significant influence on CR or OR rates were: bulky disease (absence), disease status at R-ESHAP (first PR or relapsed disease), aaIPI (0-1), and number of R-ESHAP cycles (>2). Analyzing separately the R+ group, we observed a very low CR and OR rates in patients who had primary refractory disease at the time of R-ESHAP (8% and 33%, respectively), as compared to patients who were in first PR (41% and 86%) or who had relapsed disease (50% and 75%) (p<.01 in both cases). Overall, 98 out of 163 pt underwent ASCT after the salvage therapy. With a median follow-up of 29 months (6-84), the actuarial 5-year progression-free survival (PFS) and overall survival (OS) were 38% and 50%, respectively. Patients in the R+ group had a significantly worse PFS (17% vs 57% at 4 years) and OS (38% vs 64% at 4 years) as compared with patients in the R- group. Prior exposure to R was also an independent prognostic factor for both PFS (RR: 2.0; 95% CI: 1.2-3.3; p=.008) and OS (RR: 2.2; 95% CI: 1.3-3.9; p=.004) in the multivariate analysis.

Conclusions: Our results show the efficacy of R-ESHAP prior to ASCT for refractory or relapsed DLBCL. A significant number of patients who were not refractory to upfront R-based chemotherapy respond again to R-retreatment. However, prior exposure to R was associated with a poor PFS and OS, as compared with R-naïve group.

217 LONG-TERM FOLLOW-UP OF TAXOL AND TOPOTECAN PLUS RITUXIMAB (TTR) FOR PATIENTS WITH RELAPSED AND REFRACTORY B-CELL NON-HODGKIN'S LYMPHOMA

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Background: The goal of salvage chemotherapy in patients with relapsed or primary refractory B-cell non-Hodgkin's lymphoma (NHL) is to optimize remission status prior to autologous stem cell transplant (ASCT). This study evaluated the efficacy and safety of Taxol and Topotecan plus Rituximab (TTR) as a novel salvage regimen in patients with relapsed or primary refractory NHL.

Methods: 72 eligible patients (pts) with up to 2 previous treatments not containing rituximab, taxane, or topotecan were enrolled. Rituximab 375mg/m^2 IV was given on day 1, paclitaxel 200mg/m^2 IV on day 2, and topotecan 1mg/m^2/day IV on days 2-6 in 3-week cycles with G-CSF support. After 2 to 6 cycles, responding pts were offered ASCT. This single-arm phase II study assessed 70 pts for treatment response and toxicity. 32 (45%) pts were primary refractory, and 20 pts (28%) had received prior platinum-based regimen. Primary endpoints were overall survival (OS) and event-free survival (EFS).

Results: Of 70 evaluable pts, 31 (44%) received ASCT. 21 pts (30%) responded but did not receive ASCT. Non-responders were offered additional salvage therapy as tolerated. Initial intent-to-treat analysis was performed in 2003. Median follow-up for current analysis is 70 months (mos). Overall response rate was 70%, with 42% complete response (CR). Response was 45% for pts with prior platinum therapy and 80% for pts without prior platinum therapy. EFS for all pts was 16.1 mos (95%CI 7.4, 29.2). EFS was 3.5 mos (CI 2.8, 5.9) for all pts in non-ASCT group; 7.4 mos (CI 5.0, 30.2) for responders who did not receive ASCT. EFS for ASCT group was not reached (NR). OS for all pts was 38.7 mos (CI 19.5, NR). OS for non-ASCT group was 13.6 mos (CI 10.3, 21.9); 21.7 mos (CI 13.6, NR) for responders who did not receive ASCT. OS for ASCT group was not reached. The differences in EFS and OS between ASCT and non-ASCT groups were statistically significant (p<0.0001). Grade 3/4 toxicities were neutropenia (62%), thrombocytopenia (53%), and neutropenic fever (30%).

Conclusion: Salvage therapy with TTR had significant response rate, even among pts who failed prior platinum-based therapy. This regimen when combined with ASCT is highly effective, as median EFS and OS were not reached in a median follow-up of 70 mos. Hematologic suppression was the most significant toxicity.

218 EARLY RELAPSES AND FAILURE TO ACHIEVE COMPLETE REMISSION ARE THE MAIN PROGNOSTIC FACTORS IN CD20 DIFFUSE LARGE B-CELL LYMPHOMAS (DLBCL) TREATED WITH R-ICE OR R-DHAP FOLLOWED BY STEM CELL TRANSPLANTATION IN THE CORAL STUDY

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In relapsing pts with DLBCL, improvement in response rate of salvage chemotherapy with rituximab may improve the treatment with autologous stem cell transplantation (ASCT). In the CORAL trial, DLBCL CD 20+ in first relapse or pts refractory after first line therapy were randomized between rituximab plus DHAP and R-ICE. Responding pts received (BEAM) and ASCT were randomized between observation and maintenance with rituximab every 2 m. for 1 year. The interim analysis was performed on 194 pts (100 R ICE arm, 94 R DHAP arm): median age 55 yrs; 86 relapses >12months, 108 refractory/early relapses; 97 pts with prior exposure to rituximab; Stage 3-4 107 pts; elevated LDH 88 pts; secondary IPI 0-1, 112 pts, sIPI 2-3, 63pts. The ORR was 68%, with 41% CR. Factors affecting significantly (p<.0001) response rate were: refractory/relapse < 12 months 52% vs 88 %, secondary IPI >1 54% vs 77%, prior exposure to rituximab 54% vs 82%. Pts with prior rituximab exposure had significantly more refractory disease with more adverse prognostic factors. In a logistic regression model only refractory/early relapse and secondary IPI remain significant for response rate. Only 107 pts received, per protocol ASCT. For pts transplanted, 2 years EFS was 75% (CI 63-84%) with OS 89%. Two years EFS was affected by: prior treatment with rituximab, 34% vs 66% (p=.0001); refractory/early relapse 36% vs 68% (p <.0001); secondary IPI 2-3:39% vs 0-1: 56% (p=.03).

Conclusion: Salvage chemotherapy incorporating rituximab provide a high 82% response rate in pts not previously treated with rituximab. Pts with early relapses or refractory after treatment including rituximab have a poor response rate and prognosis.

219 RESULTS AND PROGNOSTIC FACTORS AFFECTING SURVIVAL IN PATIENTS WITH RELAPSED DIFFUSE LARGE B-CELL NON-HODGKIN'S LYMPHOMA PROGRESSING AFTER AUTOLOGOUS STEM-CELL TRANSPLANTATION

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We analyzed overall survival (OS), time to progression (TTP) and prognostic variables for patients (pts) with diffuse large B-cell non-Hodgkin's lymphoma who relapsed after autologous stem-cell transplantation (ASCT). Seventy-one pts, 43 males and 28 females with a median age of 49 years (range 18–70) treated between 1993 and 2007 and reported to the GEL/TAMO Cooperative Group were retrospectively analyzed. Forty-nine pts had Ann-Arbor stage III/IV, 25 presented B symptoms and International Prognostic Index (IPI) was 3/4 in 28 pts. Thirty-four pts (47.9%) received rituximab (Rtx) at relapse postransplantation. Eighteen pts underwent a second transplantation (9 autologous, and 9 allogeneic). The median time from ASCT to relapse was 9 months (range 2-90.1). Overall response (OR) rate after progression post-ASCT was 49.3% (36.6% CR). In 34 pts who received rtx-based protocols, the OR rate was 70.6% (55.9% CR). Factors with significant influence on remission rates were: achievement of CR after ASCT (RR: 8.0) and therapy with Rtx-regimens (RR: 5.4). The median survival time from ASCT failure was 9 months with a median TTP of 4.1 months. Actuarial OS and event-free survival (EFS) at 5 years were 23.6% and 15.3%, respectively. By multivariate analysis, exposure to Rtx (RR: 1.8), high-risk IPI (RR: 5.2) at relapse, and achievement of CR after salvage treatment (RR: 1.7) were prognostic factor significantly influencing OS and EFS. In our experience, although these pts have generally a dismal prognosis, one-quarter experienced a prolonged survival. Since response to treatment post-ASCT predict the clinical outcome, newer therapeutic strategies including rituximab-based regimens should be investigated to improve the management of this group of pts.

220 TREATMENT OF HIGH RISK RELAPSES OF AGGRESSIVE LYMPHOMA BY ALLOGENEIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION INTERIM ANALYSIS OF THE DSHNHL R3 STUDY

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High dose therapy (HDT) followed by autologous stem cell support has poor outcome in patients with primary progressive aNHL or relapse after previous HDT. Allogeneic SCT (alloSCT) may help by exerting a GVL effect. We initiated a randomized phase II study using intermediate conditioning (Fludarabine 125 mg/m^2, Busulfan 12 mg/kg and cyclophosphamide 120 mg/kg) followed by GVHD prophylaxis with short term mycophenolat mofetil plus tacrolimus. Patients were randomized to receive rituximab post transplant or no further GVHD prophylaxis. From January 2005 to August 2007 sixty patients with aggressive NHL were enrolled. Thirty one patients had DLBCL, 9 patients FL grade 3, 8 patients blastic MCL, one patient transformed MZL, and 11 patients PTCL. The median number of prior treatment regimens was 3 (range 1 to 6). 43 (72%) patients had received at least one cycle of HDT with autologous SCT prior to alloSCT; 58% of patients had chemo-refractory disease and 52% had progressive disease with aaIPI high or im-high immediately prior to conditioning. Allo-PBPC were obtained from HLA-identical siblings in 16 patients, from fully matched unrelated donors in 32 patients and from mismatched unrelated donors in 12 patients. Engraftment of leukocytes was rapid and all patients achieved complete donor type chimerism after alloSCT. Median observation time is 8 months (range 1-35 months). 32 patients died, in 20 patients death was attributed to treatment related causes. After one year, estimated overall survival is 47%, failure free survival is 43%, TRM is 37%, relapse rate is 33% and incidence of GVHD > grade 1 is 57%. TRM ist mostly attributed to GVHD and infection. There was a trend to lower relapse rates in patients with GVHD > grade 1 (25% vs 44%, p=0.14). The incidence of TRM is high as in most series of alloSCT in aNHL patients. However, intermediate intensity conditioning followed by allogeneic SCT is a valuable treatment option in patients with high-risk relapse of aggressive NHL.

221 EFFICACY AND SAFETY OF LENALIDOMIDE IN RELAPSED/ REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

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Introduction/Background: Patients (pts) with diffuse large B-cell lymphoma (DLBCL) not cured by R-CHOP chemotherapy or high-dose chemotherapy with autologous stem cell rescue have a poor prognosis and represent an unmet medical need. We investigated the activity and safety of the immunomodulatory drug lenalidomide (LEN) as a monotherapy in relapsed/refractory DLBCL.

Materials and methods: Pts with relapsed/refractory DLBCL with measurable disease after ≥1 prior treatment were eligible. Pts received 25 mg LEN orally once daily (Days 1–21 every 28 days) and continued therapy for 52 weeks as tolerated or until disease progression. Response and progression were evaluated using the IWLRC methodology.

Results: Twenty-six pretreated pts with DLBCL were enrolled. The median age was 66 (45–86) years (yrs) and 13 were female. Median time from diagnosis to LEN was 2.3 (0.4–12) yrs, and the median number of prior treatment regimens was 3 (range, 1–6). Five pts (19%) had a response (1 complete response (CR) and 2 unconfirmed CR), and 7 had stable disease. Median progression-free survival (ongoing) was 3 months. Eight pts (31%) required at least one dose reduction with a median time to first dose reduction of 1.8 (0.4–2.9) months. The most common grade 3 or 4 adverse events were neutropenia (23%), and thrombocytopenia (19%).

Conclusion: Lenalidomide is active with manageable adverse events in patients with relapsed/refractory DLBCL who were heavily pre-treated.

222 RELAPSE AND CURRENT SALVAGE STRATEGIES AFTER PRIMARY R-CHO(E)P

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We analyzed survival after lymphoma related treatment failure (LF) from first line chemotherapy (CT) or immune-chemotherapy (ICT) within DSHNHL clinical trials in agg. NHL (MINT, German patients and RICOVER 60). The MINT-trial included young low risk patients. German patients were randomized to 6 cycles of CHOEP with (n=147) or without Rituximab (R) (n=144). The RICOVER 60 trial included elderly pts of all risk groups. Patients received either six or eight

cycles of CHOP with (n=610) or without (n=612) R. Within the MINT population, LF occurred in 48 pts after CT and in 24 pts after ICT. Relapse from CR (32%) and early treatment failure (PR, NC, PD, 68%) were equally distributed in both groups. After primary progression, outcome was poor with an OS of 29% (ICT) and 15% (CT) after 20 months (p=0.276). Patients with an relapse after achieving a remission had a much more better prognosis with an OS of67% (ICT) and 80% (CT) after 20 months. Within the RICOVER-60 population, LF occurred in 191 pts after CT and in 110 pts after ICT. 222 patients with LF received salvage therapy. The decision to give salvage therapy was made more often in pts with relapse (85%) than in those with early treatment failure (65%). Rituximab was part of the salvage therapy in 131 pts (59%) and HDT followed by autologous stem cell transplantation was used in 28 pts (13%). After primary progression, outcome was poor (OS at 20 months 5% to 16%) without significant differences between primary treatment arms. After relapse OS at 20 months (34% to 53%) was much better. There was a trend to a better survival after relapse from CT than from ICT. Rituximab as part of salvage therapy had a positive impact on survival after treatment failure from CT (OS 20 mo 24% vs 52%, $p < 0.001$) as well as after primary ICT (19% vs 37%, $p = 0.011$). Consolidation with HDT and ASCT in second line showed no impact after primary ICT but seems to improve outcome after CT (OS 20 mo 40% vs 66%, p=0.019). Rituximab as part of salvage therapy in agg. NHL has a positive impact on OS after failure from chemo- as well as from immune-chemotherapy.

223 VINCRISTINE DOSING IN TREATMENT OF NON-HODGKIN LYMPHOMA (NHL)

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Introduction: Vincristine (V) is a standard component of treatment for NHL. The neurotoxicity seen in the original MOPP regimen for Hodgkin lymphoma led to a recommendation to cap the dose of V at 2 mg. Despite the reduction in number of V doses from 12-24 in original MOPP to 6-8 in CVP, many centres continue to cap. The practice of capping results in lower relative dose for larger patients. With our current understanding of the importance of dose intensity (RDI) this practice should be questioned.

Methods: Patients enrolled on a trial of an idiotype vaccine for follicular NHL were treated with eight cycles of CVP. Those with a response sustained for 6 months were eligible to proceed to the vaccine trial. Participating centres could use a V dose of 1.4mg/m^2, or the same dose with a cap of 2 mg. Primary data were obtained from the trial sponsor, including patient BSA, actual doses delivered and response assessments immediately and at 6 months after chemotherapy. V toxicity data were inferred from dose reductions in V. Patients were grouped according to intent to cap V dose. Incidence of V dose reduction, actual delivered dose and relative dose intensity were compared across the groups. Overall response rates (ORR) at completion of CVP and at 6 months were compared between the two groups using standard chi-squared tests.

Results: Dosing data were available for 551 patients. 452 had V dose capped at 2 mg (capped group, CG), and 99 received 1.4mg/m^2 (non-capped group, NCG). Incidence of V dose reduction was 35% in CG and 53% in NCG (p= 0.001). Patients receiving at least 16 mg total dose was 64% in CG and 78% in NCG (p= 0.004). Response data were available for 426 patients. ORR were 86% in CG and 78% in NCG (p=0.18). Regardless of dose cap group, ORR were 86% if there was dose reduction and 88% if no dose reduction (p=0.7). Considering RDI, ORR was 84% in both the highest and the lowest RDI decile.

Conclusions: The practice of using full dose V was associated with a higher incidence of dose reduction, however, higher RDI were achieved. RDI of V did not affect ORR. These data suggest that capping V dose might decrease toxicity without sacrificing response rates in NHL.

224 THE *ISTITUTO DEI TUMORI-MILAN* REGIMEN IS HIGHLY EFFECTIVE TO TREAT BOTH CHILDREN AND ADULTS WITH BURKITT'S LYMPHOMA

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Background: The short-term intensive-dose chemotherapy regimen originally designed for children with advanced Burkitt's lymphoma (BL) has been extended to adults in our Institute. We have thus analyzed 69 newly diagnosed BL (aged 2-76 years; median 11) to evaluate differences based on age and recognised prognostic factors.

Methods: Main patient characteristics were as follows: 51 male, 18 female; 46 were ≤ 18 years of age; stage I-III/IV 51/18; 7 exhibited CNS involvement. The chemotherapy adopted (*JCO* 2002;20:2783) included a 5-week induction phase of weekly infusions basing on VCR, CTX (500 mg/m^2, 2 doses), DOXO (50 mg/m^2), HDMTX (150 mg/Kg and 250 mg/Kg, respectively), VP16 (250 mg/m^2, 2 doses) and alternating intrathecal MTX or araC (6 injections), followed by HDaraC/cisplatin consolidation. Three adults received HD-chemotherapy and peripheral blood stem cell rescue as further consolidation for an unsatisfactory response to the planned regimen.

Results: Overall 9/69 pts suffered from disease failure after median 5 months (range 2-31). Two toxic deaths occurred (acute araC-related cardiotoxicity in a 8-year-old boy; pneumonia in a 47-year-old woman). After a median f-up of 84 months, EFS, DFS, OS at 4 years were 84 ± 4%, 86 ± 4%, and 87 ± 4%, respectively (69 evaluable pts). Factors with respect to age or stage (IV versus other) did not impair survival rates with a statistically significant difference. DFS (EFS) for 55 pts aged < 33 years and 14 ≥ 33 years were 87% (85%) and 84% (77%), respectively. Pts with CNS involvement displayed lower DFS, statistically yet not significant, compared with CNS-negative (71% *vs* 88%; p .18).

Conclusion: Our data suggest that the intensive paediatric chemotherapy regimen demonstrated to be effective and feasible in adults as well. We confirm the efficacy also in poor prognosis pts, like CNS-positive. The addition of rituximab in a subset of pts is under clinical investigation.

225 SWISS HIV COHORT STUDY (SHCS): IMPACT OF LONG TERM HAART USE AND HEPATITIS VIRUSES ON NON-HODGKIN LYMPHOMA INCIDENCE

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Background: In people with HIV (PHIV), the long-term effect of HAART on non-Hodgkin lymphoma (NHL) incidence and the relationship with hepatitis C and B viruses (HCV and HBV) are still debated.

Material and methods: DATA was collected by the SHCS between 1984 and 2006 including nearly 13000 PHIV and 75000 person-years, 37000 under HAART. Among these PHIV, 429 NHL cases were identified from the SHCS dataset and by record linkage with Swiss Cancer Registries. Age- and gender-standardized incidence was calculated and hazard ratios (HR) was estimated by Cox regression. In addition, a matched case–control study nested in the SHCS was conducted including 298 NHL cases and 889 control subjects with available information on antibodies against HCV (anti-HCV) and for hepatitis B surface antigen (HBsAg). Odds ratios (OR) were computed.

Results: NHL incidence reached 13.6 per 1000 py in 1993–1995 and declined to 1.8 in 2002–2006. HAART use was associated with a decline in NHL incidence [HR=0.26; 95% confidence interval (CI), 0.20–0.33]. Among non-HAART users, being a man having sex with men, being >35 years of age, or, most notably, having low CD4 cell counts at study enrolment (HR=12.3 for <50 versus ≥350 cells/ml; 95% CI, 8.3–18.1) were significant predictors of NHL onset. Conversely, among HAART users, only age was significantly associated with NHL risk. The HR for NHL declined steeply in the first months after HAART initiation and was 0.12 (95% CI, 0.05–0.25) 7-10 years afterwards. No relationships between NHL risk and anti-HCV (OR=1.1; 95% CI: 0.6–1.8), or HBsAg 0.6 (0.3 – 1.2) emerged.

Conclusions: HAART greatly reduced the incidence of NHL in PHIV and the influence of CD4 cell count on NHL risk. The beneficial effect remained strong up to 10 years after HAART initiation. Coinfection with HIV and HCV or HBV did not increase NHL risk in PHIV.

The detailed results have been published in Br J Cancer, 2006, 95:1598–1602 (Franceschi et al) and AIDS, 2008, 22:301–306 (Polesel et al).

226 LONG-TERM FOLLOW-UP OF RITUXIMAB AND INFUSIONAL CYCLOPHOSPHAMIDE, DOXORUBICIN, AND ETOPOSIDE (CDE) IN COMBINATION WITH HAART IN HIV-RELATED NON-HODGKIN'S LYMPHOMAS (NHL)

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Background: The combination of Rituximab plus chemotherapy (ct) is more effective than CT alone in the treatment of high grade nhl.

Objective: To report the long-term follow-up ofcde plus Rituximab in HIV-NHL.

Methods: In June 1998, we started a phase II study using infusional cde (Cyclophosphamide 187.5 mg/m^2/day, Doxorubicin 12.5 mg/m^2/day and Etoposide 60 mg/m^2/day) administered by continuous intravenous infusion for 4 days every 4 weeks and Rituximab 375 mg/m^2 i.v. on day 1. haart was given concomitantly with ct.

Results: Seventy-four patients (pts) have been enrolled. The median CD4+ cell count was 161 (range 3-691) and the median Performance Status was 1 (range 0-3). Diffuse large B-cell NHL was diagnosed in 72% of pts and Burkitt in 28%. Seventy per cent of pts had advanced stage (III-IV) disease and 57% of pts had an age-adjusted international prognostic index ≥2. Fifty-two out of 74 pts (70%) achieved a complete remission (cr), 4/74 (5%) had a partial remission and 18 pts progressed. With a median follow-up of 61 months, only 17% of CRs have relapsed and 41/74 pts are alive. The overall survival, disease free survival and time to treatment failure (TTF) at 5 years were 56%, 81% and 52%, respectively. Only one secondary tumor (acute leukemia) has been observed. No case of late pulmonary or cardiac toxicity has been reported.

Conclusions: The combination of Rituximab and cde in hiv-NHL treated concomitantly with HAART is very active. CR rate (70%) and TTF at 5 years (52%) are comparable to those observed in high grade NHL of the general population. Our data confirm that in HAART era a high proportion of HIV-NHL can be cured.

227 VEBEP REGIMEN AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN PATIENTS (PTS) WITH HD AND HIV INFECTION (HD-HIV)

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Background: The outcome of pts with HD-HIV is still poor, because the duration of complete remission (CR) is short. To improve the prognosis of HD-HIV, a feasibility study with the VEBEP regimen and radiotherapy and concomitant HAART was started in previously untreated HD-HIV pts.

Materials and methods: CT included epirubicin 30 mg/m^2/day (days 1-3), cyclophosphamide 1000 mg/m^2 (day 1), vinorelbine25 mg/m^2 (day 1), bleomycin 10 mg/m^2 (day 3) and prednisone 100 mg/m^2/day (days 1-3).

Results: Since September 2001, 52 pts have been enrolled. The median age was 41 yrs. The median CD4$^+$ cell count at entry was 258/mm^3 (range 6-887) and 54% of pts had a detectable HIV viral load. Stage III and IV disease was present in 36/52 (69%) pts. Histologic subtypes were: MC 71%, NS 17%, LD 4%, LP 2%, unknown 3%. Two toxic deaths, one due to hepatic failure in a HCV-positive pt and one due to a septic shock were observed. An absolute neutrophil count <500 was noted in 30/52 pts (58%). Grade 3-4 anemia was observed in 17/52 pts (32%) and severe thrombocytopenia in 8/52 pts (15%). Sixteen pts (31%) had febrile neutropenia with 15 documented infections in 13 pts (3 varicella, 3 bacterial sepsis, 2 bacterial pneumonia, 2 PCP, 1 cerebral toxoplasmosis, 1 esophageal candidiasis, 1 HBV reactivation, 1 HCV reactivation, 1 prostatitis). A grade 2-3 mucositis was observed in 11/52 pts (21%). CR was obtained in 35/52 pts (68%) and partial remission (PR) in 8/52 pts (15%). With a median follow up of 29 months, only 4 pts have relapsed (11%). OS and TTF at 36 months are 64% and 63%, respectively.

Conclusions: Our preliminary data demonstrate that VEBEP regimen in combination with HAART is feasible and active in pts with HD-HIV.

228 THE CAUSE OF DEATH IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS FROM THE USA INTERGROUP STUDY

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Background: The cause of death and the relationship to duration of survival following treatment in DLBCL is multifactorial. This analysis prospectively tracked the cause of death in a DLBCL immunochemotherapy trial.

Methods: 632 patients, age 60 or older, with DLBCL were randomized to CHOP with rituximab (CHOP+R)(Arm A), which was administered Day -7, -3, and two days before cycles 3, 5, and 7 (if given)), vs CHOP (Arm B) for 2 cycles beyond a CR for a total of 6-8cycles. 415 patients subsequently underwent a second randomization to rituximab weekly times four to be repeated every six months times four (Arm C) vs observation (Arm D). Study chair files were reviewed and the time and cause of death were reviewed as reported and interpreted with predefined definitions for disease, infection, pulmonary, cardiac, second malignancy, unrelated to treatment (Rx) or disease, and unknown cause. Sites were queried further when indicated for appropriate data and records.

Results: With a median follow-up of 6 years, there were 253 deaths in 546 eligible and evaluable patients. The cause of death and cumulative incidence cause specific analysis in R-CHOP/CHOP were 57(21%)/72(26%) from disease (p=0.24), 21(8%)/28(10%) unrelated to disease or Rx (P=0.18), 18(7%)/10(4%) from toxicity of treatment (p=0.09), 6(2%)/7(2%) second malignancy, and 18(7%)/16(6%) were unknown (p=0.93). Deaths from disease were most common in the first 24 months, from sepsis and pulmonary the first 6 months, and from cardiac at 4 years.

Conclusion: The most common cause of death in patients with DLBCL in the immunochemotherapy era is lymphoma. Cause-specific survival is important in addressing toxicities as well as efficacy. Future directions in patients age 60 or older should focus on new therapeutic approaches.