aggressive lymphoma

162 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 rituximab in combination with 6 cycles of CHOP-14 in the first 20 patients treated within the DENSE-R-CHOP-14 trial of the DGHML [Pfreundschuh et al., Abstract ASH 2007, 798]. 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 intermittent pneumonia, confirming other reports of intermittent pneumonitis associated with R-CHOP. Three of 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 levofloxaxine (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 received 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-14 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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163 LAMIVUDINE PROPHYLAXIS IS EFFECTIVE FOR INHIBITION OF HEPATITIS B VIRAL REACTIVATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA UNDERGOING R-CHOP THERAPY

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PROPHYLAXIS IN PATIENTS TREATED WITH R-CHOP IDENTIFIES RECURRENT 11Q24.3 ABERRATIONS


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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 prophylaxis 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.

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=0.322). The median follow up of surviving patients was 24 months. CR rate between HBsAg-positive and negative were 62.5% vs. 76.6% (p=0.637), and 2yr-OS were 100% vs. 89.5% (p=0.518), respectively.

Conclusion: These results suggest that lamivudine prophylaxis is effective for inhibition of HBV reactivation in patients with diffuse large B-cell lymphoma 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.

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Diffuse large B-cell lymphomas (DLBCL) have been sub-classified by

**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 MYC rearrangement with clinical outcome.

**Results:** Eleven cases (7.7%) harbored a MYC rearrangement and had the following clinical features: Median age 71 (54-85), 64% male; stage III/IV, 82% abnormal LDL, 27% ECOG 2; 55% bulky disease (> 10cm); 36% high risk IPI (4, 5). The 4-year survival was significantly worse in patients with a DLBCL tumour MYC rearrangement (60% vs 36% p=0.006). Three patients had a central nervous system relapse. Further analysis of a subset of DLBCL using MCIF showed that the prognostic significance of myc deregulation is independent of the IPI or treatment with rituximab (p=0.012). There was a trend to a worse overall survival in cases which had an extra copy of MYC (n=46, p<0.05).

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

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**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 node tissues were stained using multi-colour immunofluorescence (MCF) to define the normal expression profiles of CD10, BCL6, MUM-1 and FOXP1. 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 MCF.

**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 PI3K immunophenotype (PI3K+P121) was classed as aberrant in all cases. 782/1407 (56%) cases of DLBCL had a GC phenotype and of these 767/782 (91%) cases were aberrant. Further analysis of a subset of DLBCL using MCF 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 37/49 (76%) 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 MCF which allows effective discrimination between co-expression of markers and multiple subpopulations of cells within the tumour.

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**188 HIGH SKP2 EXPRESSION IS AN INDEPENDENT PREDICTOR OF UNFAVORABLE OUTCOME IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMAS (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, BCL6, MUM-1, and FOXP1). Expression data were correlated with survival. The survival benefit of both low Bcl-2 and high Bcl-6 expressions diminished in combined treatment with R to CHOEP. 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 CHOEP-R. Interestingly, even in CHOEP-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 CHOEP. 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.

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

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The survival benefit of both low Bcl-2 and high Bcl-6 expressions diminished in combined treatment with R to CHOEP. 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 CHOEP-R. Interestingly, even in CHOEP-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 CHOEP. 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.
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-II, either CD40-positive (n=60) or CD40-negative (n=36), as determined by immunohistochemistry, were examined using spotted 53K 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-regulated in the CD40 positive cohort, and coded for proteins involved in cell-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, aPAP, proteasome beta type 3).

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 sulfate chains, the results of which will be presented at the conference.

191 HYPOXIA INDUCIBLE FACTOR (HIF)-1 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 12% 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 (p=0.009, 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 aberrantly 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 lymphomas 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 STNF-R2 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%, respectively. 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 3p13 (1 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. 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-CELL LYMPHOMAS: SIGNIFICANCE OF IMMUNOHISTOCHEMICAL EXPRESSION AND METHYLATION STATUS

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Background: Loss of 0’-methylguanine-DNA-methyltransferase (MGMT) expression and promoter DNA hypermethylation of MGMT promoter has been proposed as a 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.

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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 are associated with a significant decrease in event-free survival (EFS) in patients with BL treated on the International Pediatric LBL 96 study. DLEU1 is a gene located on 13q and was identified within the Burkitt classifier. Deletions of 13q have been associated with a significant decrease in event-free survival. In the current study, we investigate the expression of DLEU1 in diffuse large B-cell lymphoma (DLBCL) as a possible predictor of survival.

Methods: We examined paraffin embedded tissue specimens of 73 patients with BL or DLBCL treated at our institution. Expression of DLEU1 was determined using immunohistochemistry. The clinicopathologic factors were recorded and survival analysis was performed using the Cox proportional hazards model.

Results: In BL, there was a significant correlation between high expression of DLEU1 and improved survival (log rank p=0.005). In DLBCL, there was no significant correlation between expression of DLEU1 and survival. The median follow-up time for BL was 36 months (range 12-96 months) and for DLBCL was 31 months (range 12-96 months).

Conclusion: The expression of DLEU1 may be a predictor of survival in BL but not in DLBCL.

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 activation is high in the activated B cell-like (ABC) subtype of DLBCL and may function as a tumor suppressor gene. 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 (range 5-90), male sex 40%, IPI 0 (0), IPI 1 (19), IPI 2 (4%), IPI 3 (18%), IPI 4 (18%). Survival was 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 12 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, OS 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 mutations 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 physiological processes such as invasion and metastasis. In the current study, we investigated the expression of Ets-1, a transcription factor involved in invasion and metastasis, and also is associated with angiogenesis, cell migration, and tumor invasion. Therefore, we investigated, by immunohistochemistry, the expression of Ets-1, in diffuse large B-cell lymphoma (DLBCL) in order to demonstrate a correlation between the expression of this gene and other prognostic factors.

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

Results: 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 CMYCASSOCIATED 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 BCL2 and cMYC rearranged, and 16 (7%) had t(14;18) and BCL6 rearranged and of these 7 had 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.

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 lowcytometry. 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, TNFx, 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, angiogenin 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, PFG2 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.
were categorized into four different responsive groups according to the interim PET/CT and CT: 1) Complete metabolic response (CMR)-CRu, 2) CMR-partial response (PR), 3) partial metabolic response (PMR)-CRu, and 4) PMR-PR.

Results: The median age was 57 years, with 42.2% of 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, 79% of patients with PMR-PR experienced a relapse during or after the completion of chemotherapy. We also found significant differences between patients with PMR-CR (31.1% and 29.2%) and CMR-CR (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 in interim PET/CT and CT were independent prognostic significances for OS with a hazard ratio (HR) of 2.98 (1.15 – 7.23) and 1.22 (1.16 – 1.29), respectively. Moreover, disease bulk (≥19 cm) and PMR-PR showed significant associations for EFS with a HR of 3.73 (1.49 – 9.53) 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-HODGKIN LYMPHA: REVIEW OF LITERATURE

Introduction/Background: Investigators reported early PET/CT positivity (+) to be a strong predictor of progression free (PFS) and 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 & rituximab. This generated 15 articles discussing 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 &/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.

Conclusion: Investigators have reported that PET/CT negativity early in therapy is a more 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 therapy. 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 analyzed (standardized uptake value, SUV) and correlated with outcome (median follow-up 20 months). 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 none 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 SUVmax yielded a sensitivity of 100% but a specificity of only 38%.

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-CHOP 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 (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.

Methods and Materials: 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 have 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, 1 IPI risk factor: good, 2 IPI risk factors: poor). Median follow-up was 45 months, with a range of 7 months to 146 months. Overall survival (OS) with the IPI was 94%, 76%, 61% and 53%, and with the R-IPI it 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 risk categories with a statistically significant improvement in survival over 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-CALGB505013

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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 showed a PFS and OS of 76% and 96% respectively with a median follow-up of 4.5 years with no progressions beyond 2 years following therapy. PFS is 91%, 67% and 47% in IPI subgroups of 0-2, 3, and 4-5 risk factors, respectively, at 4.5 years (JCO submitted).

Materials and 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 significant advantage for CHOP with 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, and CHOP followed by rituximab 375 mg/M2 weekly times 4, repeated every six months times 4 (MR) vs. CHOP only. All pts were observed for a minimum of 1 year. The primary endpoint was FFS and OS were estimated applying 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=0.04). 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=0.06) and 36% (95% CI, 0.28, 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 administered 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 (32% vs 35%).

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


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Background: Our research has demonstrated in various forms of non-Hodgkin’s lymphomas (NHL) that the sum of [Etn-P]+/NTP and [Etn-P]+/Cho-P/NTP ratio predicts long-term failure in diffuse large B-cell lymphoma (DLBCL). We have reported that the [Etn-P]+/Cho-P/NTP ratio may be a useful predictor of treatment failure.

Methods and materials: 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. Ninety-five patients were diagnosed to have de novo CDS-positive DLBCL (R-CHOP). 54 of 91 (median: 66) years old. Rituximab was added to the chemotherapy in 85 patients. Of the 112 in the chemotherapy, 52 were positive for CDS and 74 were negative. For patients treated without rituximab, overall survival (OS) of CDS-positive and –negative group were not different (5-year OS: 50% vs. 49%, p=0.72). However, for patients treated with rituximab, CDS-negative group showed better prognosis as compared with CDS-positive group (3-year OS: 84% vs. 59%, p=0.04). Prognosis of CDS-positive group did not improve after the introduction of rituximab.

Conclusion: Rituximab improves prognosis of CDS-negative DLBCL when combined with standard chemotherapy, but not for CDS-positive DLBCL. Further strategies are required to remedy the poor prognosis of CDS-negative DLBCL.
**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 diffuse large B-cell lymphoma (DLBCL). However, many pts aged 70 years (yrs) or more are often considered poor-risk patients. The aim to evaluate feasibility and activity of a CGA-driven CT for elderly pts with DLBCL.

**Methods:** In high-risk patients treated with R-MegaCHOP induction, those who only 2 had relapsed. In the early PET negative group, the 3-year LFS was significantly better 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 yrs (18–60 yrs), 23 had WHO PS 2-4, 41 had LDH level >N and 38 had stage III or IV disease. The age-adjusted IPI was 23 in 23 and was high in 19 yrs. The program was completed in 30 pts (71%): there were 3 toxic deaths, 8 treatment failure and 1 A1 disease. 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 remission. Two with a poor score (ADL<5 and IADL<5) received 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 IPI or high adjusted IPI DLBCL with a 5-year OS of 74% and is currently being compared with classical CHOP-R regimen. Late toxicity is very acceptable.

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**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:** Superiority of HDT with autologous stem cell transplantation (ASCT) in the upfront treatment of poor-risk DLBCL remains an option for intermediate-high (II) or high IPI young adults. We updated results of the prospective trial GoRams 07a 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 III or high adjusted IPI, to the age of 60 yrs. This program consisted of 2 courses of high-dose CHOP-like regimen with Rituximab, followed by a course of high-dose methotrexate with cytarabine. 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 yrs (18–60 yrs), 23 had WHO PS 2-4, 41 had LDH level >N and 38 had stage III or IV disease. The age-adjusted IPI was 23 in 23 and was high in 19 yrs. The program was completed in 30 pts (71%): there were 3 toxic deaths, 8 treatment failure and 1 A1 disease. 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 remission. Two with a poor score (ADL<5 and IADL<5) received 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 IPI or high adjusted IPI DLBCL with a 5-year OS of 74% and is currently being compared with classical CHOP-R regimen. Late toxicity is very acceptable.
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 TIER-3 HIGH-GRADE NON-HODGKIN-LYMPHOMA STUDY GROUP (DSHNL)

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Background: Application of peg-fs 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 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 pts, 51 received peg-f on day 2 (D2) and 52 on day 4 (D4). D2 and D4 administrations were well balanced for known risk factors, and there was no difference between pts. receiving chop-14 and D2 which regard 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. Leukopenia (<2000/mm3) lasted for 3 (day 8 to 10) after D2 and 1 day (day 9) after D4. Grade 4 leukopenia (<1000/mm3) occurred in 13% of all cycles after D2 and in 20.5% after D4 (p=0.001). Grade 3.10.18. There were 4 therapy-associated deaths (all infection-associated) in the D2 and 1 (infection-associated) in the D4 group (p=0.020 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 leukopenia, less infections and less therapy-associated deaths. An analysis whether the favorable end-high infectious profile of D4 application translated into better outcome will be presented. Supported by Angen

218 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: 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/m2 IV was given on day 1, paclitaxel 200mg/m2 IV on day 2, and topotecan 1mg/m2/day IV on days 2-6 in 3-week cycles. Primary endpoints were overall response rate (ORR), event-free survival (EFS), and overall survival (OS). Results: Of 70 evaluable pts, 31 (44%) received ASCT. 21 pts (30%) responded but did not receive ASCT. No-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% of complete response (CR). Response was 45% with 32% (p<0.0001) for both ASCT and non-ASCT groups. 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 (HR 2.95; CI 1.3-3.3; p=0.038) and OS (HR 2.29; CI 1.3-3.8; p=0.004) 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 b-cell chemotherapy respond to R-ESHAP. However, prior exposure to R was associated with a poor PFS and OS, as compared with R-naive group.
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 POE trial, CR 26% 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 2-4 months for 1 year. The interim analysis was performed on 194 pts (100 R ICE arm, 94 R DHAP arm): median age 55 yrs; 86 yrs; relapse >12months, 108 refractory/early relapses; 97 pts with prior exposure to rituximab; Stage 3A-4 107 pts; elevated LDH 88 pts; secondary I PI 0-1 112 pts; I PI 2-3 63pts. The ORR was 68%, with 41% CR. Factors affecting significantly (p<.001) response rate were: refractory/relapse <12 months 52% vs 88%, secondary I PI 0-1 54% vs 77%, prior exposure to rituximab 54% vs 82%. Pts with prior rituximab exposure had significantly worse event-free survival (EFS) and overall survival (OS). Pts with prior rituximab exposure had significantly more adverse events with more adverse progression. Model only refractory/early relapse and secondary I PI remain significant for response rate. Only 107 pts received, per protocol ASCT. For pts transplanted, 2 years EFS was 73% (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 I PI 2-3 vs 3-39% vs 61. 36% (p<.003).

Conclusion: The 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 AUTLOGOUS STEM-CELL TRANSPLANTATION

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We analyzed overall survival (OS), time to progression (TPP) 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 GE/L-TAMO Cooperative Group were retrospectively analyzed. Forty-nine pts had Ann-Arbor stage III/IV, 25 presented B symptoms and International Prognostic Index (I PI) was 3/4 in 28 pts. Thirty-four pts (47.9%) received rituximab (Rtx) at relapse posttransplantation. Eighteen pts underwent a second transplantation (9 autologous, and 9 allogeneic). The median time from ASCT to relapse was 9 months (range 2–90). Overall response (OR) rate after progression pre-ASCT was 43% (36.6% CR). In 34 pts who received rtx-based protocols, the CR 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 I PI (RR: 5.2) and relapse after ASCT were independent prognostic factors significantly influencing OS and EFS. In our experience, although these pts have generally a dismal prognosis, one-quarter experienced a prolonged survival. Since relapse is an indicator of higher tumour burden, we may 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 ALLOGENIC PERIPHERAL BLOOD STEM CELL TRANSPLANTATION INTERIM ANALYSIS OF THE DSHNL R3 STUDY

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High dose therapy (HDT) followed by autologous stem cell support has poor outcome in patients with primary progressive aNH or relapse after previous HDT. Allogeneic SCT (allograft) may help by exerting a GVL effect. We initiated a randomized phase II study using intermediate conditioning (Fludarabine 125 mg/m², Busulfan 12 mg/kg and cyclophosphamide 120 mg/kg) followed by GVHD prophylaxis with short term methylprednisolone mitrol 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, 1 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; 34% of patients had chemo-refractory disease and 52% had progressive disease with aIPI high or high-immediately prior to conditioning. Allo-PBPC were obtained from HLA-identical siblings in 16 patients, from fully matched 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 is mostly attributed to GVHD and infection. There was a trend to lower relapse rates in patients with GVHD > grade 1 (25% vs 46%, p=0.14). The incidence of TRM is high as in most series of alloSCT in aNH 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 2 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 IWCLC 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 (0–12) 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-CHOEJP

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We analyzed survival after lymphoma related treatment failure (LF) from first line chemotherapy (CT) or immune-chemotherapy (ICT) within DSHNL clinical trials in agy. NHL (MINT, German patients), and BIOGPS (R-CHOEP). The DSHNL 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 MIP-388 population, the CR rate was 32% and 34% for patients receiving CHOP with or without R (p=0.15). A retrospective analysis of 325 patients revealed that a higher CR rate was achieved in patients receiving chemotherapy with R compared to those receiving chemotherapy alone (60% vs 40%, p=0.001). Treatment-related mortality was lower in the group receiving chemotherapy with R (2% vs 7%, p=0.04).
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 immunochemothrapy 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, -5, and -4, and two days before cycles 1, 2, and 7 (if given), vs CHOP (Arm B) for 2 cycles beyond a CR for a total of 6-8 cycles. 415 patients subsequently underwent a second randomization to rituximab weekly times four to be repeated every sixth 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 235 deaths in 546 eligible and evaluable patients. The cause of death and cumulative incidence cause specific analysis in R-CHOP (CHOP+R) (Arm A), which was administered Day -7, -5, and -4, and two days before cycles 1, 2, and 7 (if given), vs CHOP (Arm B) for 2 cycles beyond a CR for a total of 6-8 cycles. 415 patients subsequently underwent a second randomization to rituximab weekly times four to be repeated every sixth 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.

Conclusions: The most common cause of death in patients with DLBCL in the immunochemothrapy 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.