450 CONSOLIDATING RADIOTHERAPY IN HIGH-RISK NON-HODGKIN'S LYMPHOMA: STILL AN APPEALING CONCEPT!

D.A. Grootenboers[1], M. van de Pol[1], P.M. Poortmans[1]
[1]Radiotherapy, Dr. Bernard Verbeeten Institute, Tilburg, Netherlands

Introduction: The primary treatment for stage ≥ II aggressive non-Hodgkin's lymphoma (NHL) consists of 6 to 8 cycles of chemotherapy. The role of consolidating radiotherapy for high-risk patients is uncertain. Therefore, we retrospectively analysed the outcome of all our patients consecutively treated with curative intent with consolidating radiotherapy after chemotherapy.

Methods: We treated 181 patients from 1972 to 2005 for stage ≥II NHL. The vast majority (160 patients) was irradiated as part of initial combined modality treatment. Of those patients, 76 had a complete response and 84 had residual disease after chemotherapy. Another 21 patients were irradiated after salvage chemotherapy for recurrent disease. All patient files were evaluated and updated if necessary.

Results: Median age at the time of radiotherapy was 61 years (range 9 – 83); 105 were male en 76 female. The median follow-up time for surviving patients is 4.7 years (0.3-33). Radiotherapy was given according to the ''iceberg principle'' and to the ''involved field'', ''extended field'' and ''involved nodal'' concepts or to residual disease only in 49 (27%), 100 (55%), 4 (2%), 18 (10%) and 10 (6%) patients, respectively. The 5 year overall survival is 63% in the initially irradiated group with a CR after chemotherapy, 58% in the initially irradiated group with residual disease and 35% in patients irradiated for a recurrence. Disease free survival at 5 years is 61%, 60% and 37%, respectively. In 28 out of the 73 patients who developed a recurrence, the disease recurrence was at least partially within the original radiation field. The acute radiotherapy related toxicity was grade 1 or less in 145 patients (80%), grade 2 in 34 (19%) and grade 3 in 2 patients. Late toxicity was not reported.

Conclusions: The outcome of our patients in this non-selected group of high-risk NHL treated with consolidating radiotherapy after chemotherapy compares favourably with the results as published in the literature. Radiotherapy-related toxicity was very mild. The presence of residual disease after chemotherapy and the radiotherapy technique had no influence on the outcome but patients who were treated for recurrent disease experienced a worse prognosis.

451 THE EFFECT OF DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) TREATMENT REGIMENS ON SURVIVAL: A PROSPECTIVE COHORT STUDY

M. Sieniawski[1], T. Mainou-Fowler[1], J. Wilkinson[1], D. Culligan[1], J. Davison[1], J.R. Goodlad[1], G. Jackson[1], H. Lucraft[1], J. Lewis[1], A. Lennard[1], P. McKay[1], D. Miekeljohn[1], R. Prescott[1], J. White[1], S.J. Proctor[1]
[1]Haematological Sciences, Newcastle University, Newcastle upon Tyne, United Kingdom, On Behalf of Scotland and Newcastle Lymphoma Group

Background: Most data on treatment and outcome of DLBCL patients (pts) come from clinical trials on selected groups of pts. However, data on large unselected cohorts is still unavailable.

Material and Methods: DLBCL pts prospectively registered in SNLG between 1990 and 2003 were evaluated. Further inclusion criteria were: age at diagnosis ≥18 years and primary nodal origin of disease; pts treated with Rituximab were excluded.

Results: 1863 pts were included (median age 66 years (y), range 18-98y); 711 pts were ≤60y and 1152 >60y; 49% pts were male. Anthracycline based chemotherapy (CT) was the most frequently used treatment (75%), followed by radiotherapy (RT) alone (7%), other CT (6%) and autologous stem cell transplantation (ASCT) in 1st remission (5%); 7% of patients received no CT or RT. Among pts ≤60y there were statistically significant more males, pts with lower ECOG and IPI, and fewer pts with bone marrow involvement and abnormal Hb-, albumin- and urea-level as compared with pts >60y; $p<0.05$. Progression free survival (PFS) and overall survival (OS) at 5y for all pts were 33% and 42%, respectively. 5y PFS was highest in pts treated with anthracycline based CT (37%) and in pts with ASCT (36%), followed by pts with RT only (29%) and lowest in pts with other CT and in pts without CT and RT (both 10%); $p<0.05$. 5y OS was highest in pts with ASCT (61%), followed by pts treated with anthracycline based CT (46%) and pts with RT only (41%) and lowest in pts with other CT (14%) and in pts without CT and RT (10%); $p<0.05$. 5y PFS and OS were higher in pts ≤60y and in pts with CSI and II; $p<0.05$. Using the IPI, 4 different groups were distinguished with 5y PFS and OS of 55% $p<0.05$.

Conclusions: The outcome of unselected DLBCL pts in the pre-Rituximab era was unsatisfactory, especially in high-risk and elderly pts. Prognostic value of IPI was limited in high-risk groups. The question of whether the addition of Rituximab to standard therapy has improved the outcome in all or in only some group of pts needs to be evaluated in unselected cohorts of pts.

452 FACTORS INFLUENCING TIME TO INITIATION OF CHEMOTHERAPY IN ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

M. Danese[1], M. Gleeson[1], C. Reyes[2], M. Pao[2], K. Pao[3]
[1]Epidemiology and Outcomes Research, Outcomes Insights, Inc., Newbury Park, United States, [2]Health Economics, Genentech, Inc., South San Francisco, United States, [3]Medicine, California Pacific Medical Institute, San Francisco, United States

Background: DLBCL is an aggressive lymphoma for which treatment should be initiated quickly. The purpose of this study is to identify factors associated with the initiation of chemotherapy and the incremental cost of care.

Methods: We analyzed DLBCL patients diagnosed from 1998 to 2002 with 1 year of non-HMO coverage prior to diagnosis in the SEER-Medicare dataset. Time to initial chemoimmunotherapy (CT) and costs of care were identified through claims for inpatient, outpatient and physician services through 2005. Costs were compared to a random sample of non-cancer Medicare patients using linear regression. Time to CT was assessed using proportional hazards regression with censoring for death and end of coverage. Models were adjusted for age, race, gender, comorbidity score, year of diagnosis, region (cost model) and stage (time model). CT was classified using all outpatient claims after diagnosis.

Results: There were 4,716 patients identified. The mean age at diagnosis was 77 years, 86% were white, 31% were stage IV and 53% were alive 12 months after diagnosis. The mean monthly cost for the first year after diagnosis was $8,003 higher in DLBCL patients than in typical Medicare patients. Only 71% of patients received CT within the follow up period. Median time to first CT was 57 days. The most common initial CT used was CHOP+R (63%). Older age and greater comorbidity burden were associated with longer times to first CT ($p<0.01$). Black and other race were also associated with a significantly longer time to first CT ($p<0.01$).

Conclusions: DLBCL is associated with an increased incremental cost of care. The time to CT initiation was associated with several patient characteristics including age and race.

453 ULTIMATE OUTCOMES OF PATIENTS WITH RECURRENT DIFFUSE LARGE B CELL LYMPHOMA WHO DO NOT RESPOND TO SECOND-LINE CHEMOTHERAPY

R.L. Elstrom[1], P. Martin[1], J. Barrientos[1], A. Chadburn[2], R. Furman[1], J. Ruan[1], T. Shore[1], M. Schuster[1], M. Coleman[1], J. Leonard[1]
[1]Medicine, Weill Cornell Medical College, New York, United States, [2]Pathology, Weill Cornell Medical Center, New York, United States

Background: Patients with diffuse large B cell lymphoma (DLBCL) who relapse after or are refractory to initial therapy can in some cases experience long term disease free survival after second-line chemotherapy alone or followed by autologous stem cell transplantation. The major predictor of outcome for patients undergoing autologous transplant is response to prior (second-line) chemotherapy. Patients not responding to second-line regimens may receive third-line or subsequent chemotherapy regimens in hopes of achieving response and proceeding to transplant, but available outcome data from this group are limited.

Methods: We used pathology and treatment records to identify patients with recurrent DLBCL (excluding transformed lymphoma) at Weill Cornell Medical Center for whom data on response to second-line chemotherapy could be determined. An online social security database verified survival. Median overall survival (OS) was calculated by the Kaplan-Meier method.

Results: Sixty patients with relapsed or refractory DLBCL who underwent second line chemotherapy were identified. Chemotherapy consisted of ifosfamide-containing regimens in 54 patients (90%), platinum-containing regimens in 49 (82%) and included rituximab in 25 (42%). Thirty-nine patients (65%) achieved at least partial response (R), while 21 patients (35%) did not respond (NR). Median OS was 4 months (range 1-74) in the NR group, and 57 months (range 3-108) in the R group. Only 4 patients in the NR group (19%) survived for greater than one year. Of 19 NR patients who underwent third-line therapy, only 2 of 13 with available response data achieved a clinical response and underwent autologous transplantation. One patient remained in remission for 3 months, with OS 7 months, while the other patient is alive in remission 72 months after transplant.

Conclusion: Patients with recurrent DLBCL who do not respond to second-line chemotherapy have poor outcomes, with only rare patients achieving extended survival following subsequent chemotherapy. Clinical trials of novel therapeutic regimens should be prioritized as management strategies for these patients.

454 ABSTRACT WITHDRAWN

455 IMMUNOHISTOCHEMICAL EXPRESSION PATTERN OF GERMINAL CENTER AND NON-GERMINAL CENTER MARKERS CORRELATES WITH PROGNOSIS IN NODAL DIFFUSE LARGE B-CELL LYMPHOMA IN PERU

B. Beltran[1], D. Morales[2], P. Quiñones[2], L. Riva[3], F. Hurtado de Mendoza[3], A. Carrasco-Yalán[1]

[1]Onco Hematology, Hospital Edgardo Rebagliati Martins, Lima, Peru, On Behalf of Latin American Onco Hematology Cooperative Group (LACOHG), [2]Pathology, Hospital Edgardo Rebagliati Martins, Lima, Peru, [3]Onco Hematology, Hospital Edgardo Rebagliati Martins, Lima, Peru

Background: Recent studies have shown correlations between diffuse large B-cell lymphoma (DLCBL) prognosis and molecular features using genome profiles by cDNA microarrays. Since this analysis is not routinely used, immunohistochemical tests for prediction of DLBCL survival are gaining major importance, using markers as, CD10, BCL-6 and MUM-1 to identify germinal center B-cell (GCB) and non-GCB, respectively. The main objective of this study was to evaluate the significant effect on survival within GCB and non-GCB subgroup.

Patients and Methods: Fifty-two pts with nodal DLBCL de novo diagnosed in a single institution were included. Tissue microarrays (TMA) blocks were created from paraffin-embedded, formalin-fixed block and stained with antibodies to CD20, CD10, BCL-6 and **MUM1**. The statistical method was descriptive and survival was calculated using the Kaplan-Meier method.

Results: Fifty-two pts (median age: 68 yrs: 29M/236F). All cases received chemotherapy based in CHOP regimen. Cases were subclassified using CD10, BCL-6, and **MUM1** expression, and 15 cases (33.8%) were considered GCB and 37 cases (66.2%) non-GCB. Non-CGB in comparison with GCB had poor zubrod (p=0.007), high lactyc deshidrogenase (p=0.049), higher IPI (p=0.043) and less complete response to chemotherapy (p=0.032). Five year overall survival was 79% and 23% for GCB and non GCB respectively (p=0.015). In univariable analysis, zubrod, lactyc deshidrogenase, IPI and GCB/non GCB were independent prognostic factors.

Conclusion: Immunohistochemical expression of CD10, BCL-6 and **MUM1** are able to determine the GCB and non-GCB subtypes of nodal DLBCL and predict survival.

456 EXPRESSION OF CD43 IS AN IMPORTANT NEGATIVE PROGNOSTIC MARKER IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

Z. Mitrovic[1], I. Ilic[2], M. Nola[2], I. Aurer[1], S. Basic-Kinda[1], I. Radman[1], R. Ajdukovic[3], S. Dotlic[2], B. Labar[1]

[1]Hematology, University Hospital Center and Medical School, Zagreb, Croatia, [2]Pathology, University Hospital Center and Medical School, Zagreb, Croatia, [3]Hematology, University Hospital Dubrava, Zagreb, Croatia

Introduction: CD43 is a membrane protein expressed on all leukocytes except resting B-cells with a postulated role in adhesion and T-cell activation. Expression of CD43 is an unfavorable prognostic marker in extranodal marginal zone B-cell lymphomas. CD43 is expressed in 20-30% of DLBCL but its prognostic significance is unknown.

Methods: We studied the expression of CD43 and its prognostic significance in 101 patients with DLBCL receiving front-line anthracycline-based chemotherapy, 52 of whom received also rituximab. Response was assessed by standard criteria.

Results: CD43 was expressed in 25 patients (25%). The median follow-up of survivors was 36 months. CD43+ patients had significantly lower complete response rates (56% vs. 84%, p<0.001), inferior event-free survival (EFS) (26% vs. 66% at 2 years, p<0.001) and overall survival (OS) (44% vs. 71% at 2 years, p=0.001) than CD43- patients. The prognostic impact of CD43 was not affected by rituximab treatment. CD43 expression was not related to IPI score, stage, LDH, age, performance status or GCB vs. non-GCB type as determined by immunohistochemistry but was related to the number of involved extranodal sites (p=0.031). The prognostic impact of CD43 expression was of the same order of magnitude as that of IPI.

Conclusions: The expression of CD43 in patients with DLBCL identifies a subgroup of patients with significantly inferior response rates, EFS and OS. This effect is independent of the IPI score or rituximab treatment. There are no clear biological explanations for the adverse effect of CD43 in lymphomas. While it is possible that CD43 expression facilitates adhesion and migration of lymphoma cells to extranodal sites, this does not seem to be the whole explanation of its significant prognostic impact.

457 PROGNOSTIC INFLUENCE OF BCL-2 EXPRESSION IN DIFFUSE LARGE B-CELL NON-HODGKIN'S LYMPHOMAS TREATED WITH THE R-CHOP REGIMEN

F. Gaudio[1], A. Giordano[1], T. Perrone[1], C. de Risi[1], A. Guarini[1], M. Delia[1], A. Napoli[2], R. Ricco[2], G. Specchia[1], V. Liso[1]

[1]University of Bari, Hematology, Bari, Italy, [2]University of Bari, Pathology, Bari, Italy

Diffuse large B-cell lymphoma (DLBCL) is a heterogeneous entity and patients exhibit a wide range of outcomes. BCL2 protein expression has been associated with poor prognosis in patients with DLBCL. The addition of rituximab to CHOP chemotherapy (R-CHOP) has led to a marked improvement in survival and has cast doubt on the significance of previously recognized prognostic markers. We performed a retrospective analysis of 111 patients with de novo DLBCL treated at our institute between 2000 and 2005, to assess the value of BCL2 expression in the era of immunochemotherapy. Histological diagnoses were established according to the REAL-WHO classification. HIV-associated lymphomas, transformed lymphomas, cases with central nervous system involvement, primary mediastinal and primary extranodal DLBCL were excluded. Tumors were considered positive when at least 50% of tumor cells expressed bcl-2 protein. All patients received CHOP every 3 weeks; 58 patients were treated with chemotherapyplus rituximab (R-CHOP) and 53 patients with chemotherapy alone (CHOP). There were 68 (61%) bcl-2+ patients and 43 (39%) bcl-2- patients. The response rates for R-CHOP and CHOP were 71% and 59% (p<0.05) in bcl-2+ patients and 74% and 72% (p=n.s.) in bcl-2- patients, respectively. At a median follow-up of 3 years, R-CHOP was significantly associated with a better overall survival than CHOP in bcl-2+ patients (79% versus 48%, p<0.05). In bcl-2- patients there was no statistically significant difference in terms of overall survival (75% versus 68%, p=n.s.). In addition, R-CHOP was associated with significantly better progression-free survival rates than CHOP in bcl-2+ patients (fig1.b: 65% versus 38%, p<0.01) but not in bcl-2- patients (60% versus 40%, p=n.s.). Multivariate analysis confirmed the significant benefit on survival and progression-free survival of R-CHOP in bcl-2+ patients. These results suggest that the addition of rituximab to CHOP chemotherapy offsets the adverse prognostic influence of BCL-2 protein expression on progression free and overall survival in DLBCL.

		R-CHOP	CHOP	
BCL2-	OS	75%	68%	p=n.s.
	PFS	60%	40%	p=n.s.
BCL2+	OS	79%	48%	p<0.05
	PFS	65%	38%	p<0.01

458 P57KIP2 GENE METHYLATION IS USEFUL TO DETECT MINIMAL RESIDUAL DISEASE IN DIFFUSE LARGE B CELL LYMPHOMA

H. Nagai[1], K. Hagiwara[1], M. Hamaguchi[1], T. Hotta[1]

[1]Clinical Research Center, National Hospital Organization Nagoya Medical Center, Nagoya, Japan

In diffuse large B cell lymphoma (DLBCL), the universal method for evaluation of minimal residual disease (MRD) in bone marrow has not been established. The BCL2/IgH gene rearrangement is usually used to detect and quantify MRD in follicular lymphoma (FL), but the frequency of this rearrangement is relatively low in DLBCL. The analysis of CDR III region of IgH is not also applicable for all cases of DLBCL. We revealed that the promoter region of p57KIP2 gene is frequently methylated in DLBCL. Aberrant DNA methylation in the promoter regions of genes is known as the major mechanism for inactivation of tumor suppressor genes, thus such methylation is expected to be a promising tumor specific marker. Therefore, we investigated the possibility of p57KIP2 gene promoter methylation as a marker for MRD detection in DLBCL.

Methods: We analyzed lymphoid cell line DNA, tumor DNA from 64 patients with DLBCL and 4 patients with FL, and 11 peripheral blood mononuclear cells (PBMNCs) from healthy volunteer. The bisulfite-modified DNA was used as a template for real-time quantitative methylation-specific PCR (Q-MSP).

Results: In clinical samples (tumor DNA), p57KIP2 gene methylation was detected by Q-MSP in 72% (46/64) DLBCL, 50% (2/4) FL, 0% (11/11) in normal PBMNCs. Using cell line DNA, which was fully methylated in promoter region of p57KIP2 gene, we determined the detection limit of Q-MSP assay. The methylated DNA could be detected in the presence of a 10000-fold excess of unmethylated DNA by Q-MSP. In calculation, it meant the possibility to detect 0.6-0.8 genome per one reaction. The sensitivity to detect MRD by this method was found to be equivalent to real time quantitative PCR for BCL2/IgH major breakpoint region.

Conclusion: The methylation of p57KIP2 gene is detected at high frequency in DLBCL. The sensitivity to detect MRD by this method is shown to be equal to quantitative PCR for BCL2/IgH. This method is thought to be conventional and widely applicable to the detection of MRD in DLBCL.

459 P63 PROTEIN EXPRESSION IN HIGH RISK DIFFUSE LARGE B-CELL LYMPHOMA

A.E. Hallack Neto[1], S.A. Siqueira[1], F.L. Dulley[1], B. Beitler[1], M. Belesso[1], L.F. Pracchia[1], D.A. Chamone[1], J. Pereira[1]

[1]Haematology, University of São Paulo, São Paulo, Brazil

Introduction: The importance of p63 protein for diffuse large B-cell lymphoma (DLBCL) is still unclear from the pathological and clinical perspective. In order to better understand this protein and improve the prognostic evaluation of DLBCL patients with high intermediate to high age-adjusted International Prognostic Index (aIPI) risk, the impact of p63 expression on achieving complete remission (CR), disease-free survival (DFS) and overall survival (OS) was studied in correlation with markers associated to the cell origin in the germinal center (GC) or out of germinal center (NGC).

Material and methods: Seventy-three patients aged under 60 years old were examined by immunohistochemistry using a monoclonal antibody p63 clone 4A4 clone.

Results: The authors found that subset of DLBCL 37 (50.7%) were positive when we considered threshold of 10% of neoplastic cell and 11(15.1%) when the threshold were 50% of neoplastic cell. When only patients showing more or iqual of cells were considered positive, there were statistically significance for DFS (p=0.016) for patients with more that 50% of positive cells than cases with less 50% positive cells to p63.

Conclusions: Despite their controversy, our results showed that p63 expression can be used in the risk stratification of DLBCL patients with high intermediate to high aIPI risk.

460 REDUCED DOSE OF NON-PEGYLATED LIPOSOMAL DOXORUBICIN WITH CYCLOPHOSPHAMIDE, VINCRISTINE AND PREDNISONE ± RITUXIMAB FOR PREVIOUSLY UNTREATED ELDERLY PATIENTS WITH AGGRESSIVE LYMPHOMA NON SUITABLES FOR STANDARD CHEMOTHERAPY

E. Gimeno[1], A. Álvarez[1], C. Pedro[1], E. Abella[1], M. Gomez[2], J. Comin[2], B. Sanchez[1], C. Besses[1], A. Salar[1]

[1]Hematology, H Mar, Barcelona, Spain, [2]Cardiology, Hmar, Barcelona, Spain

Background: CHOP± Rituximab® is the standard regimen for elderly patients (pts) with aggressive lymphoma but many of them are not fitted for it due to associated comorbidities. The aim was to evaluate retrospectively the efficacy and safety of a modified-CHOP (reduced dose non-pegylated liposomal doxorubicin (NPLD)± R in elderly pts with aggressive lymphoma not tributary to standard chemotherapy.

Patients and Methods: Retrospective analysis of 16 pts with previously untreated aggressive lymphoma. Median age 76 years (62-85). Seven pts stage I-II(IPI1-2) and 9pts stage IV(IPI2-5). Median LVEF 60.2%(31-80). Comorbidities: liver disease (2 pts, 1pts hepatocellular carcinoma), chronic obstructive pulmonary disease (3 pts), cardiomiopathy (4 pts) and others (7 pts). Schedule: NPLD 30 mg/m^2, cyclophosphamide 750 mg/m^2, vincristine 1.4 mg/m^2,prednisone 100 mg/d d1-5± R 375 mg/m^2 d1 every 21 days, pegfilgrastim d2.

Results: Fifteen pts are evaluable for efficacy (1pts is on active treatment). Median number of cycles was 4 (range 4-6). A complete response (CR/uCR) was achieved in 11pts (84.6%) (in 1pts, the CR was achieved after radiotherapy) and partial response in 2pts (15.4%). Two pts due to infectious complications and 3pts relapsed during follow-up at 3, 5 and 13 months respectively, all dying with active disease. OS at 12 months 75% (95%CI 53-97) and PFS at 12 months 67% (95%CI 43-91), median time of follow-up for surviving pts of 16.6 months (4.9-28.3). Treatment was well tolerated with grade III-IV neutropenia in 16.6% of cycles and 4 hospital admissions for febrile neutropenia. No other relevant toxicities were observed. Therapy was delayed in 8.3% of cycles. LVEF was not significantly different before and after treatment with 1pts showing a significant improvement in his LVEF.

Conclusion: This preliminary data indicate that reduced dose NPLD in modified CHOP regimen is an active and well tolerated treatment in patients with severe comorbidities and formal contraindications to receive standard therapy. Further exploration of this regimen administered every 14 days is warranted.

461 SIGNIFICANT DOSE ESCALATION OF IDARUBICIN IN THE TREATMENT OF LOW RISK AGGRESSIVE NON-HODGKIN'S LYMPHOMA LEADS TO INCREASED HEMATOTOXICITY AND DECREASED EFFICACY: NINE YEAR FOLLOW UP OF A PHASE-I/II TRIAL OF THE DSHNHL

K. Hohloch[1], C. Zwick[2], M. Zeipert[2], U. Kaiser[2], A. Engert[2], M. Reiser[2], H. Hoeffkes[2], F. Kroschinsky[2], R. Meesters[2], A. Feller[2], M. Leoffler[2], L. Truemper[2], M. Pfreundschuh[2]

[1]Haematology/Oncology, University of Goettingen, Goettingen, Germany, [2]Saarland University, DSHNHL, Homburg/Saar, Germany

A Phase I/II dose esc. study substituting Idarubicin (Id) for doxorubicin (D) in the CHOEP-14 regimen to determine the Id dose with equal hematotoxicity compared to D was performed. Long term follow up data for toxicity and efficacy were assessed.

Methods: Pts (PS 0-3, BM inv. <25%, normal CBC, age 18-75 y.) with aggr. B-NHL received 6 cycles of CIVEP-14:Id 11-16 mg/m^2 d1, cyclophosphamide 750 mg/m^2 d1, vincristine 2mg d1, etoposide 100 mg/m^2 d1-3 and prednisone 100 mg d1-5, G-CSF d 5-13.

Results: Between 11/96 and 09/98, 64 pts from 7 centres were included, 9 pts had to be formally excluded at the final evaluation. 55 pts, median age 56 (23-71), were evaluated, median observation time for OS of 9.3 yrs. 78% of pts had IPI 0/1, 13% IPI 2, 4% IPI 3 and 5% IPI 4/5. 22% had bulky disease, 54.5% extranodal disease. Id dose could be escalated to a max. of 16 mg/m^2 (24 pts). Treatment had to be terminated earlier than planned in 8/55 pts due to toxicity. CR-rate was 77.4% (95%-CI 66.1-88.7%). The 5 and 8-yr-EFS rates are 46.4 (32-60%) and 43.5 (29-67%), the 5 and 8 yr OS rates are 64.6 (52-77%) and 59.9 (46-73%). 14/55 pts have died due lymphoma PRO, and 2/55 pts (4%) due to treatment related toxicity, 4/55 due to non-treatment related complications (3 late infections, 1 acute heart failure), for 3 pts. cause of death is not known. Increase in other long term toxicity was not observed.

Conclusion: The Id/D hematologic equivalency is 1.5 to 5 rather than 1 to 5; Id was therefore underdosed in previous trials. Compared to CHOEP-14, hematotoxicity is higher and lymphoma control with a published 5 year EFS of 40.2/69.4 (32-48/ 62-77%) in the elderly/younger pts and a 5 year OS of 49.8/85.1 (41-58/79-90%) in the NHL B2/1 trial for CHOEP-14, inferior esp. for the younger pts. The Id dose increase does not translate into higher efficacy but increases hematotoxicity. Therefore Doxorubicin remains the standard anthracycline for the treatment of aggressive NHL.

462 IN DIFFUSE LARGE B CELL LYMPHOMA PATIENTS R-CHOP14 SEEMS TO OVERCOME THE NEGATIVE PROGNOSTIC SIGNIFICANCE OF B CELL ORIGIN

L. Rigacci[1], B. Puccini[1], S. di Lollo[2], M. Doria[2], L. Nassi[1], R. Alterini[1], V. Carrai[1], F. Bernardi[1], A. Bosi[1]

[1]Hematology, Azienda Ospedaliera Universitaria Careggi, Florence, Italy, [2]Pathology, Azienda Ospedaliera Universitaria Careggi, Florence, Italy

Approximately half of all patients with diffuse large B cell lymphoma will be cured of their disease by primary therapy the remaining die of the disease. Gene-expression profiling identified two major subgroups: germinal centre B (GCB) cell or non-germinal centre (non-GCB). In some recent papers the GCB group showes a significantly better survival than non-GCB group. Immunohistochemistry (IHC) has been evaluated as a surrogate for this molecular classification. The aim of this study was to define retrospectively the B-cell origin of 35 patients (pts) treated with R-CHOP14 and to evaluate if the dose-dense immuno-chemotherapy could improve their clinical outcome. We performed IHC stains on formalin-fixed paraffin-embedded tissues from diagnostic biopsies and based on the algorithm published by Hans et al. we subdivided the pts in GCB origin and non-GCB origin. Twenty-four pts were male, 18 were stage III-IV, 17 showed bulky disease. Eighteen pts showed abnormal LDH value, the IPI was intermediate-high risk in 9 and high risk in 4 pts. According to IHC analysis 15 pts derived from germinal centre and 20 from non-germinal centre, 17 pts presented a positive bcl2. Twenty-five pts (71%) obtained a CR, 7 a PR and 3 were NR. All pts with PR and 2 out 3 NR derived from germinal centre. Four out 25 CR pts experienced relapse, three (75%) derived from non-germinal centre. Eight pts died five derived from non-GCB. After a median period of observation of 13 months (range 3-65 months) the overall survival (OS) was 71% and the failure free survival (FFS) was 57%. The statistical analysis was performed comparing the B cell origin and clinical characteristics. In univariate analysis normal Beta2 microglobulin and ESR, low-intermediate risk IPI were significantly associated with longer OS. The FFS was significantly higher in low and low-intermediate IPI risk patients it was the only factor that influenced the FFS. In conclusion even if few patients were evaluated we can point out that the intensification could improve the OS in patients with non-GCB lymphoma. Further analysis with larger sample sizes of DLBCL pts are needed to verify this preliminary observations.

463 FCGR3A POLYMORPHISMIS NOT RELATED TO CLINICAL OUTCOME AFTER INITIAL R-CHOP THERAPY IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

E. Kisiel[1], P. Centkowski[1], K. Owczarska[1], M. Lewandowska[1], W. Jurczak[2], E. Kalinka-Warzocha[3], M. Sobocinski[2], M. Majewski[1], K. Warzocha[1]

[1]Department of Hematology, Institute of Hematology and Blood Transfusion, Warsaw, Poland, [2]Department of Hematology, Jagiellonian University of Cracow, Cracow, Poland, [3]Department of Proliferative Diseases, Regional Oncology Center, Lodz, Poland

Introduction: The addition of rituximab to CHOP chemotherapy (R-CHOP) improved survival of patients with diffuse large B-cell lymphoma (DLBCL). Antibody-dependent cellular cytotoxicity (ADCC) is thought to be a predominant mechanism of rituximab activity in clearance of lymphoma cells. ADCC is mainly mediated by Fc gamma receptor (FCGR) and several studies suggested that FCGR polymorphism can influence antitumor efficacy of rituximab. The aim of this study was to determine the possible impact of FCGR3A polymorphism on the outcome in 31 patients with DLBCL initially treated with R-CHOP.

Methods: Polymorphism within FCGR3A locus, including FF, VF, and VV alleles was determined by allele-specific PCR. End points were overall response rates (ORR), including complete (CR) and partial remissions (PR), progression free (PFS) and overall survival (OS).

Results: The distribution of FCGR polymorphic alleles was 35% of FF, 52% VF, and 13% VV. ORR were 90.8% in FF, 93.7% VF, and 100% in VV carriers, including 54.5%,

68.7%, 50% CR and 36.3%, 25%, 50% PR, respectively. Treatment responses, PFS, and OS didn't differ significantly between studied groups.

Conclusions: These data indicate that initial response to R-CHOP in the studied group of DLBCL patients was not related to FCGR3A polymorphism.

464 EFFICACY OF CONVENTIONAL SECOND-LINE SALVAGE THERAPY IN PATIENTS WHO HAVE PROGRESSIVE DISEASE AFTER FIRST-LINE SALVAGE THERAPY WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

M. Kodaira[1], M. Yokoyama[1], M. Oooka[1], H. Asai[1], K. Ueda[1], S. Yamada[1], T. Myojo[1], Y. Mishima[1], S. Sakajiri[1], K. Takeuchi[1], S. Sakajiri[1], K. Takeuchi[2], T. Saotome[1], Y. Terui[1], S. Takahashi[1], K. Hatake[1]

[1]Medical Oncology / Hematology, Cancer Institute Hospital, Tokyo, Japan, [2]Pathology, Cancer Institute of JFCR, Tokyo, Japan

Introduction: ICE, DHAP and ESHAP are considered conventional platinum-containing salvage therapy for relapsed or refractory diffuse large B-cell lymphoma. The optimal treatment for progression after 1st line salvage therapy is not standardized.

Methods: We retrospectively analyzed the efficacy of conventional platinum-containing salvage regimen as 2nd line salvage therapy for diffuse large B-cell lymphoma.

Results: The outcome of 20 patients (M:F=13:7) (median age=62, 28-76) with diffuse large B-cell lymphoma, who have previously received conventional salvage therapy, was analyzed. Sixteen of the patients were treated adding rituximab to conventional salvage therapy. In all 20 patients, responses were six with complete remission (CR) and two with partial response (PR), resulting in 42.1% of overall response (ORR). With median follow up of 10.5 months, estimated 1yr-progression free survival (PFS) was 27.0% and 1 yr-overall survival (OS) was 55.7%. Four patients who were potential candidates for autologous stem cell transplantation (ASCT) were able to receive ASCT. Seven patients (63.6%) of 11 patients who had response after 1st line salvage therapy responded to 2nd line salvage therapy, including three patients with CR. In contrast, one of the nine patients (11.1%) who had no response after 1st line salvage therapy responded. No statistical differences were observed in OS between responders and non-responders to 1st line salvage therapy, but 1-yr OS was predisposed to be higher for responders than non-responders (57.0% versus 16.7%).

Conclusion: Patients with progression disease after response to 1st line salvage therapy can be salvaged with platinum-containing 2nd line salvage therapy, while the patients not responded to 1st line salvage have poor prognosis. In conclusion, the patients with progression disease without response to conventional salvage therapy should be considered alternative therapy.

465 RADIOIMMUNOTHERAPY WITH ^{131}I-RITUXIMAB FOR RELAPSED DIFFUSE LARGE B CELL LYMPHOMA: A PHASE II STUDY PRELIMINARY REPORT

M.F. Leahy[1], A.D. McQuillan[1], J.H. Turner[1]

[1]The University of Western Australia, Fremantle Hospital, Fremantle, Australia

Aims: Radioimmunotherapy (RIT) with ^{131}I-rituximab is effective treatment of relapsed and refractory indolent non-Hodgkin Lymphoma with an overall response rate (ORR) of 76% and complete remission (CR) in 53%. The role of RIT in relapsed Diffuse Large B Cell Lymphoma (DLBCL) is less clear. Our single institution phase II study to treat 40 patients was designed to assess the efficacy and safety of ^{131}I-rituximab in patients unsuitable for aggressive chemotherapy and/or BMT.

Methods: Patients with relapsed or refractory DLBCL received induction with 4 once weekly 375 mg/m^2 rituximab doses and a single individualized ^{131}I-rituximab therapy activity predicated upon 0.75Gy whole body radiation absorbed dose on an outpatient basis. Lugols iodine was administered to prevent thyroid irradiation. Consolidation therapy commenced day 56 and continued bi-monthly with unlabelled rituximab 375 mg/m^2 for 6 treatments. Patients were monitored with weekly blood counts until recovery from nadir. Follow up PET/CT scans were performed at 6, 12, 24 and 52 weeks post treatment.

Results: Twelve patients have been enrolled. Nine patients have received treatment with ^{131}I-rituximab with an additional treatment imminent prior to planned interim safety analysis. Eight patients are evaluable for response. Two patients had a severe deterioration in performance status following enrolment and were not treated. Four patients achieved CR. 2 confirmed at 6 weeks and one each at 3 months and 6 months with PFS of 26, 21, 8 and 5 months. One patient had stable disease at 6 weeks. Three patients with PD had median IPI score of 3 and raised LDH compared with the responder's median IPI 2 and normal LDH. Grade 4 neutropenia occurred in one patient. There was no grade 4 thrombocytopenia. All 9 treated patients had had prior rituximab. Three of the responders had had refractory disease.

Conclusions: Treatment with ^{131}I-rituximab may potentially provide effective and safe therapy in some patients with relapsed DLBCL who may be elderly or otherwise not suitable for intensive chemotherapy or BMT. Patients with refractory and/or rapidly progressive and bulky disease are least likely to respond to radioimmunotherapy.

466 ROLE OF RITUXIMAB IN THE FIRST LINE THERAPY OF HIGH RISK DLBCL – A POLISH LYMPHOMA RESEARCH GROUP (PLRG) RETROSPECTIVE MULTICENTER ANALYSIS

W. Jurczak[1], J. Wegrzyn[1], A. Giza[1], D. Krochmalczyk[1], B. Stella-Holowiecka[2], A. Holowiecka-Goral[3], M. Swierczynska[4], J. Walewski[4], G. Mazur[5], T. Wrobel[5], E. Kalinka-Warzocha[6], P. Boguradzki[7], E. Kisiel[8], P. Centkowski[8], W. Knopinska-Posluszny[9], T. Gromek[10], J. Smok-Kalwat[11], A.B. Skotnicki[1]

[1]Dept of Hematology, Jagiellonian University Teaching Hospital, Krakow, Poland, On Behalf of PLRG, [2]Hemat, SLAM, Katowice, Poland, [3]Hemat, SLAM, Katowice, Poland, [4]Clin.Oncol., COI, Warszawa, Poland, [5]Hemat, Medical University, Wroclaw, Poland, [6]Clin.Oncol., Medical University, Łodz, Poland, [7]Hemat, SP CSK AM, Warszawa, Poland, [8]Hemat, IHiT, Warszawa, Poland, [9]Hemat, AM, Gdansk, Poland, [10]Hemat, AM, Lublin, Poland, [11]Clin.Oncol., SCO, Kielce, Poland

Background: Chemoimmunotherapy is a standard 1st line treatment for DLBCL. Most randomized studies were performed in low risk cases and CHOP-21-R is sometimes considered sub-optimal for younger high risk (IPI 3-5) pts.

Methods: 250 high risk DLBCL patients (IPI 3-5), treated in the last 5 years in 10 PLRG centers were retrospectively analyzed. Patients median age was 53 years (17–83), IPI – 3.7 (3–5), LDH 593 IU/l (186–9800 IU/l). The impact of Rituximab (n=178) and consolidation approaches (n=99) on overall and progression free survival (OS and PFS) was assessed.

Results: At 5 years there was an important superiority of Rituximab containing regimens in PFS (60% vs 30%, p=00003 in Gehan Wilcoxon test). The marginal difference in 5 year OS (72% vs 63%, p=0.1), could only be explained by the efficacy of II line salvage regimens (most relapsing cases were subjected to ASCT). Patients consolidated after the first line therapy had a mere survival benefit (5 year OS 80% vs 50%, p=0.09) almost entirely due to cases treated without Rituximab (83% 5 year 0S vs 43%, p=0.01).

Conclusion: With all limitations of retrospective analysis, it backs up the position of CHOP-R-21 as a standard therapy approach in high risk DLBCL patients. Outside clinical trials consolidation strategy should not be recommended in a Rituximab era.

467 A RANDOMIZED CONTROL CLINICAL STUDY: DNCE REGIMEN FOR TREATMENT OF ADVANCED AGGRESSIVE NON-HODGKIN LYMPHOMA

X. Liu[1], H. Wang[1]

[1]Department of Lymphoma, Tianjin Medical University Cancer Hospital, Key Laboratory of Cancer Prevention and Therapy, Tianjin, China

Introduction: DICE [dexamethasone (DXM), ifosfamide (IFO), cisplatin (DDP) and etoposide (VP-16)] regimen is one of the standard second line chemotherapy for the treatment of advanced aggressive and high agressive non-Hodgkin lymphoma (NHL). This study compares the efficacy and safety of DNCE (DXM, navelbine (NVB), DDP and VP-16) regimen and DICE regimens in the treatment of this disease so that it could provide a rationale for evident-based treatment.

Material and methods: A total of 69 patients with histopatholigically proved advanced aggressive and high agressive NHL were randomized into trial group (32 patients treated with DNCE regimen) and control group (37 patients treated with DICE regimen). The trial group was given DICE regimen: DXM 20 mg, iv d1∼d4; IFO 1 g/(m^2.d), iv d1∼d4; Mesna 400 mg, iv q8h, d1∼d4; DDP 25 mg/m^2, iv d1∼d4; Vp-16 100 mg/(m^2.d), iv d1∼d4; one cycle for 21∼28 days. The control group was given DNCE regimen: DXM 20 mg, iv d1∼d4; NVB 25 mg/m^2, iv d1 and d5; DDP 25 mg/m^2, iv d1∼d4; Vp-16 100 mg/(m^2.d), iv d1∼d4; one cycle for 21∼28 days.

Results: There was no significant differences in the complete response rate, partial response rate, and total response rate between DNCE group and DICE group (18.8% vs.16.2%, 37.5% vs. 37.8%, and 56.3% vs. 54.1%, respectively P>0.05). The 1-, 3-, and 5-year survival rates were not significantly increase in DNCE group than in DICE group (86.5% vs. 87.5%, 58.3% vs. 57.9%, 42.9% vs. 38.5%, respectively, P>0.05). The major side effects were leucopenia, thrombocytopenia, and nausea in both groups. The marrow depression in DNCE group was significant slighter than in the DICE group (P<0.05).

Conclusions: The efficacy of DNCE regimen was equivalent to DICE regimen, and the marrow toxic was less in DNCE group than in DICE regimen. So the DNCE regimen was an effective second line chemotherapy for the treatment of advanced aggressive and high agressive NHL with well tolerated toxicity.

468 MODIFIED R-DHAOX AS SALVAGE THERAPY IN PATIENTS WITH RELAPSED OR REFRACTORY DIFFUSE LARGE B-CELL LYMPHOMA

A. Fabbri[1], L. Rigacci[2], M. Lenoci[1], S. Mappa[2], B. Puccini[2], L. Nassi[2], I. Chitarrelli[1], A. Gozzetti[1], R. Alterini[2], V. Carrai[2], A. Bosi[2], F. Lauria[1]

[1]Hematology, Az. Ospedaliera Universitaria Senese, Siena, Italy, [2]Hematology, Az. Ospedaliero-Universitaria Careggi, Florence, Italy

Introduction: Standard salvage chemotherapy for aggressive NHL has not been established. DHAP has been one of the most effective and utilized regimens. This study was designed to assess the efficacy and safety of substituting cisplatin with oxaliplatin in the DHAP regimen, treatingon an outpatient basis patients (pts) with relaspsed/ refractory aggressive NHL.

Material and methods: pts were treated at three weekly intervals with Rituximab (375 mg/m^2 day 0), oxaliplatin (120 mg/m^2 day 1), cytarabine (2000 mg/m^2 administered daily on day 2 and 3, instead of twice on day 2 as reported by the original protocol) and dexamethasone (40 mg days 1 to 4). 37 pts with median age of 59 years (range 33-75) entered this study. Histological subtypes were 34 diffuse large B cell and 3 grade III follicular lymphoma.

Results: the overall response rate (RR) was 78% (29/37) including 15 complete remission (CR) and 14 partial remission (PR). 31 pts were treated with R-DHAOx as second line, 6 pts were treated with R-DHAOx as third line therapy. 10 out of 14 (71%) pts programmed to high dose therapy obtained a response and were treated with PBSCT. 11 pts were primary refractory and only 4 obtained a partial response. At univariate analysis chemosensitive disease and PS 0-1 at salvage therapy were significantly correlated with response to therapy. The majority of pts experienced severe haematological toxicity despite the use of hemopoietic growth factors, but none of them required hospitalisation. No grade 3-4 extra-hematological toxicity was reported. During a median overall survival (OS) period of 15 months (range 2-51 months) 12 pts died (32%). Probabilities of 1-year progression free survival (PFS) and OS were 34% and 41% respectively. The two factors that significantly affect OS were response to therapy and chemosensitive disease.

Conclusions: modified R-DHAOx has a clinically significant activity in relapsed/ref. chemosensitive pts with an acceptable toxicity profile; moreover the high rate of successful PBSC collection after treatment makes this regimen attractive before high-dose chemotherapy.

469 MODIFIED IMVP16 PROTOCOL IN TREATMENT OF PATIENTS WITH RELAPSE AND REFRACTORY AGGRESSIVE NON-HODGKIN'S LYMPHOMA-SINGLE CENTER EXPERIENCE

D.J. Ristic[1], N. Milanovic[1], S. Jelic[1], S. Matkovic[1], L. Pavlovic[1]
[1]*hematology, Institute of Oncology and Radiology of Serbia, Belgrade, Serbia and Montenegro*

Purpose: High-dose polychemotherapy with autologous bone marrow transplantation is standard treatment for relapse and refractory lymphoma. Due to age, poor performance status and presence of co morbid diseases significant number of patients is not eligible for this modality of treatment. In this prospective cohort we evaluated the efficacy, toxicity, and feasibility of modified salvage chemotherapy regimen in a single center setting.

Patients and Methods: We tested a modified salvage regiment protocol IMVP16 containing ifosfamide (given at dose 1000 mg/m^2 from day 1 to day 5) with mesna support and etoposide (given at dose 100 mg/m^2 from day 1 to day 3), without metotrexate in patients with relapse and refractory intermediate- and high-grade non-Hodgkin's lymphoma. Chemotherapy was repeated every third week, three to six times according to response. Fifteen patients entered the trial. The median age was 61 years. All 15 patients had stage III or IV disease. The distribution among international risk categories-low, intermediate-low, intermediate-high, and high was 6.7%, 60%, 20%, and 12.3%, respectively.

Results: Of 14 eligible patients, two (13.3%) had acomplete remission and four (26.6%) a partial remission, eight patients had progressive disease (53.3%). One patient was lost for follow up. Median time to progression was 18.5 months. After a medianobservation time of 12.5 months, the estimated time to relapse are 67% respectively. Toxicity was primarynonhematological (nausea and vomiting) with no grades III and IV. We registered one neutropenia gr IV (1/53) and two trombocytopenia gr III (2/53). There were no treatment-related deaths.

Conclusion: Our preliminary data suggests that VP-IFO regiment is relatively efficient, safe and feasible for treatment of patients with relapse and refractory aggressive non-Hodgkin's lymphoma, which are not candidates for high-dose polychemotherapy with autologous bone marrow transplantation. Further study is needed in order to confirm our results.

470 SAFETY AND EFFICACY OF R-CHOP14 IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) REDUCING GRANULOCYTE COLONY-STIMULATING FACTORS (GCS-F)

B. Puccini[1], L. Rigacci[1], R. Alterini[1], V. Carrai[1], F. Bernardi[1], A. Bosi[1]
[1]*Hematology, Azienda Ospedaliera Universitaria Careggi, Florence, Italy*

Diffuse large B cell lymphoma represents 40% of all NHLs. CHOP chemotherapy plus rituximab administered every 14 days (R-CHOP14) has been considered the standard of care for young patients (pts) with good-prognosis DLBCL (MInT trial). The RICOVER-60 trial have recently demonstrated that 6 cycles of R-CHOP-14 could be considered the new standard for elderly pts with DLBCL. Dose-dense therapy is feasible with GCS-F support which is recommended for 10 days. The aim of the study was to evaluate the feasibility and the haematological toxicity of R-CHOP14 supported by G-CSF in pts with DLBCL and to assess the possibility to reduce the number of GCS-F vials without increasing incidence of febrile neutropenia, hospedalizations and delays of therapy. We have included 45 pts with DLBCL and 5 with follicular lymphoma grade IIIb, median age was 62 years (range 34-79), 60% had an high-intermediate or high IPI. CHOP was administered every 14 days, preceded on day 1 by rituximab and followed by 7 or 5 days of G-CSF (filgastrim). Haematological toxicity and feasibility was calculated over 293 cycles administered. We have used 1246 GCS-F vials, 5 vials for cycle and a median of 25 vials (range 10-35) for every pt. The programmed therapy was completed in 48 out 50 pts (96%); two pts swichted to a different therapy. 11 cycles (3.8%) have been delayed in 9 pts for severe adverse events. Neutropenia grade 3-4 developed in 3% of cycles, febrile episodes in 1% of cycles, thrombocytopenia grade 3 or 4 in 1% of cycles and hospedalization in 1% of pts. Of the 293 cycles considered, the median nadir of leucocyte was 3785 × 10^9/L (range 700-8400), the median nadir of haemoglobin was 11.1 gr/dl (range 5.8-15.5) and the median nadir of platelets was 146000 (range 47000-328000). The complete remission rate was 84%. In conclusion in our experience, the dose dense chemotherapy (R-CHOP14) with G-CSF support was feasible also in elderly pts. The reduction from 10 to 5 GCS-F vials has not determined an increase of neutropenia, febrile episodes, delays and hospedalizations. There are insufficient data to assess the impact of G-CSF on disease-free and overall survival.

471 R-CHOP VS R-EPOCH IN DIFFUSE LARGE B-CELL LYMPHOMA CS IIBULKY–IV. THE SERBIAN STUDY LYMPHOMA GROUP (SLG) EXPERIENCE

B. Mihaljevic[1], B. Andjelic[1], S. Jankovic[1], V. Milosevic[1], A. Sretenovic[1], O. Markovic[2], P. Djurdjevic[3], L. Jakovic[1], M. Perunicic[1], N. Colovic[1], M. Petrovic[1], D. Boskovic[1]
[1]*Lymphoma Department, Institute of Hematology, Clinical Center of Serbia, Belgrade, Serbia and Montenegro, On Behalf of Serbian Lymphoma Study Group,* [2]*Hematology Department, Clinical Center Bezanijska Kosa, Belgrade, Serbia and Montenegro,* [3]*Hematology Clinic, Clinical Center Kragujevac, Kragujevac, Serbia and Montenegro*

Background: Recent international randomized studies confirmed the benefit of overall response rate (ORR) and overal survival (OS) in patients treated with anti CD20 monoclonal antibody-rituximab (R) plus conventional chemotherapy-CHOP and CHOP-like regimens. There are still about 30% of patients who relapse or are refractory to initial therapy. Several reviews showed that R+EPOCH has benefits compared to R+CHOP.

Methods: During the last 7 years period, 78 pts with newly diagnosed DLBCL with advanced Ann Arborclinical stadium (CS II bulky-IV) were treated with R + chemotherapy: 57 pts were treated with R+CHOP and 21 pts with R-EPOCH. International Prognostic Index (IPI) and bulky disease were initially determined in all pts. The median follow up was 36 months (range 1-84).

Results: The patients treated with R+CHOP had mean age 55.51±14.37 (range 23-92) yrs; 61.02% were <60 yrs, 81.25% had PS 0-1, 42.37% had bulky disease, 45.67% had CS IV, 18.64% had low IPI. The patients treated with R+EPOCH had mean age 44.14±14.17 (range 22-69) yrs; 90.48% were < 60yrs, 66.67% had PS 0-1, 33.33% had PS2, 52.38% had bulky disease, 61.9% had CS IV, 9.52% had low IPI. Patients treated with R-EPOCH were significantly younger (p=0.005) but had worse initial prognostic parameters (CSIV, PS2 and bulky disease). There was no statistically significant difference regarding the response rate (74.58% R-CHOP vs 71.43% R-EPOCH, p=0.634) and three years progression free survival (81% R-CHOP vs 77% R-EPOCH, p=0.896), but the three years overall survival was significantly higher in R-CHOP group (96.5% R-CHOP vs 71.4% R-EPOCH, p=0.002).

Conclusion: In our experience the therapy with R-EPOCH did not show benefit compared to R-CHOP. The difference between these two groups in overall survival can probably be explained by higher PS, more advanced CS, and more frequent bulky disease among pts treated with R-EPOCH.

472 RITUXIMAB RETHERAPY IN AGGRESSIVE NON HODGKIN LYMPHOMA AFTER INITAL IMMUNOCHEMOTHERAPEUTIC TREATMENT WITH RITUXIMAB

A. Borgerding[1], J. Hasenkamp[1], L. Truemper[1], B. Glass[2]
[1]*Hematology and Onkology, University Hospital Goettingen, Goettingen, Germany,* [2]*Department of Hematology, Asklepios Klinik St. Georg, Hamburg, Germany*

The efficacy of chemotherapy combined with rituximab in patients with relapsed or progressive Non Hodgkin lymphoma (NHL) after initial treatment with rituximab containing chemotherapy was evaluated. Of 17 eligible patients, ten had diffuse large B-cell lymphoma– with one having Richter's syndrome. Seven had mantle cell lymphomas. In 64% of the patients the IPI was ≥2. The median age was 55 years (36-72 years) at the time of diagnosis. 12 patients were male. Objective response to first immunochemotherapy (ICT) was seen in 12 (70.5%) patients and included complete remission in six of them. All patients with MCL had objective responses. After relapse, 58% (7/12) responded again to ICT: two had a CR and five a PR. Non responder to first line ICT did not respond to second ICT (5/5). Eight patients did not receive high-dose chemotherapy. Four responded to second ICT (CR/ PR). But within less than

12 months, 5 of these patients died due to NHL, two are alive but in progression at 12 and 34 months, one patient was lost to follow up in PR 10 months after second ICT. Nine patients received high dose chemotherapy with stem cell transplantation (SCT). Four patients received autologous or syngenic SCT, respectively. One patient with MCL is in remission 43 months after radioimmunotherapy. One patient after autologous SCT is in PD 21 months after start of second ICT, respectively 6 month after SCT. Two received a second – that time allogeneic SCT due to residual disease. CR was achieved in 6 out of 7 patients after allogeneic SCT with no signs of progression in the seventh patients. One relapse was seen in the observation time up to 11 months. But success is hampered by high mortality. Due to infections four patients died 3, 6, 9 and 26 months after allogeneic SCT without signs of NHL. At 35 and 31 months post allogeneic SCT only 2 patients are alive and in CR. In relapsed aggressive NHL second response to ICT with rituximab is seen in 58% of the patients. But the risk of further relapses is high. In these patients high-dose radioimmunotherapy and allogeneic SCT are options to induce long term remission or maybe cure.

473 3 YEARS OUTCOME OF NEWLY DIAGNOSED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL) PATIENTS TREATED WITHIMMUNOCHEMOTHRAPY– SERBIAN LYMPHOMA STUDY GROUP (SLG) EXPERIENCE

B. Mihaljevic[1], S. Jankovic[1], B. Andjelic[1], R. Jancic-Nedeljkov[1], V. Milosevic[1], A. Sretenovic[1], M. Bogunovic[1], A. Vidovic[1], M. Todorovic[1], J. Bila[1], M. Sretenovic[1], N. Colovic[1], M. Virijevic[1], O. Markovic[2], P. Djurdjevic[3], S. Sretenovic[3], L. Jakovic[1], M. Perunicic[1], M. Petrovic[1], D. Boskovic[1]

[1]Lymphoma Department, Clinical Center of Serbia, Belgrade, Serbia and Montenegro, On Behalf of Serbian Lymphoma Study Group, [2]Hematology Department, Clinical Center Bezanijska Kosa, Belgrade, Serbia and Montenegro, [3]Hematology Clinic, Clinical Center Kragujevac, Kragujevac, Serbia and Montenegro

Background: DLBCL is the most common type of Non Hodgkin lymphoma. Recent international randomized studies confirmed the benefit of overall response rate (ORR) and overal survival (OS) in patients (pts) treated with anti CD20 monoclonal antibody-rituximab (R) plus conventional chemotherapy-CHOP/CHOP-like, compared with chemotherapy alone.

Methods: During the last 7 yrs, 113 pts with newly diagnosed DLBCL were treated with R+CHOP/CHOP like regimens. On presentation the International Prognostic Index (IPI) and bulky disease were determined. The median follow up was 36 months (range 1-84 months).

Results: The mean age was 52.43±14.5 yrs, range 22-92(69% of pts were <60 yrs). Gender distribution was 63 male/50 female. 7 pts (6.19%) were in I CS, 41(36.28%) in II CS, 25(22.12%) in III CS and 40 (35.40%) in IV CS. The IPI distribution was as follows: low risk 39 pts (34.51%), intermediate risk 67 pts (59.29%) and high risk 7 pts (6.19%). Bulky disease had 36 pts (31.86%). 70 pts (61.95%) had ECOG performance status (PS) 0, 23 pts (20.95%) had PS1 and 20 pts (17.7%) had PS 2. The ORR (CR+PR) was 76.99%. CR was better in pts <60 yrs (border line significance, p=0.056) and in low/low intermediate IPI. There was no significant difference between the pts regarding CS, bulky disease and PS. Progression free survival (PFS) after 3 yrs was 84.0% and it was not influenced by CS, bulky disease and PS. PFS was better in pts <60 yrs and pts with low/low intermediate IPI (p=0.053). OS after 3 yrs was 91%. No difference between the subgroups regarding CS, IPI, PS and the presence of bulky disease was found.

Conclusion: Higher rate of CR as well as better 3 yrs PFS were achieved in younger pts (<60 yrs) and in pts with low/low intermediate IPI. According to SLG experience, immunochemotherapy showed significant improvement of the outcome of newly diagnosed DLBCL pts. CS, bulky disease and PS haven't the predictive value on the outcome, so new parameters need to be tested for predictive scoring system.

474 REDUCTION RATE OF ABSOLUTE LYMPHOCYTE COUNT AFTER R-CHOP MAY ESTIMATE SURVIVAL IN PATIENTS WITH EARLY STAGED-DLBL

S. Sohn[1], J. Kim[1], Y. Chae[1]

[1]Hematology, Kyungpook National University Hospital, Daegu, Korea, Republic of

Background: Although the International Prognostic Index (IPI) or absolute lymphocyte count (ALC) was known as a prognostic factor in DLBL, those have not been confirmed in the rituximab era. We evaluated prognostic factors for survival in patients with early staged-DLBL after R-CHOP treatment.

Methods: From Aug. 2003, 77 patients with early staged DLBL, who finished R-CHOP as scheduled according to NCCN guidelines, were retrospectively reviewed. Survival analysis were performed according to clinical parameters (age, performance status, LDH, extranodal involvement, stage, ALC, and difference rate of WBC or ALC).

Results: Among 77 patients with early staged DLBL, 25 patients (32.5%) were classified as stage I. All but 5 patients presented with a good performance status and LDH was elevated in 20 patients (26.0%). According to IPI, 66 (85.8%) cases were classified in the low-risk group, 8 (10.4%) in the low-intermediate group, and 3 (3.9%) in the high-intermediate risk group. The overall response rate was 100% including 94.8% complete response (CR). Survival analysis demonstrated that a difference rate of ALC after the 1st R-CHOP treatment was the only factor associated with progression-free survival (p=0.049) and response duration (p=0.049), whereas age was the single most important prognostic factor for overall survival (p=0.014).

Conclusion. Although there might be some limitations, our data showed the strong prognostic value of the difference of ALC on survival after R-CHOP treatment. Because ALC is simple to perform as a routine test, the evaluation for difference of ALCs after R-CHOP will be warranted.

475 CLINICAL CHARACTERISTICS AND SURVIVAL ANALYSIS OF LBL PATIENTS TREATED WITH CHOP-BASED REGIMENS ALONE OR WITH CONSOLIDATION HIGH DOSE TREATMENT AND HSCT

Y.K. Shi[1], Y. Qin[1], X.H. He[1], X.H. Han[1], S.Y. Zhou[1], J.L. Yang[1], S. Yang[1], C.G. Zhang[1], Q.L. Wang[1], F.Y. Feng[1], Y. Sun[1]

[1]Medical Oncology, Institute & Hospital, Chinese Academy of Medical Sciences, Beijing, China

Purpose: Retrospective analysis of the clinical characteristics and survival of lymphoblastic lymphoma (LBL) patients treated with CHOP-based regimens alone or followed by consolidation high-dose treatment and hematopoietic stem cell transplantation (HDT-HSCT).

Experimental Design: From 1989 to 2004, a total of 63 patients with LBL/ALL were treated with at least 2 cycles of standard CHOP-based regimens as initial therapy in our Hospital. Among the 63 patients, 26 received consolidation HDT-HSCT, including 23 autologous and 3 allogeneic HSCT.

Results: The median age of the 63 patients was 20 years old. Fifty-seven (90%) cases were diagnosed of T-LBL/ALL and 6 (10%) were B-LBL. Fifty-six (89%) patients had stage III–IV diseases. Bone marrow involvement presented in 18 (29%) patients. Nine (14%) had central nervous system involvement. With a median follow-up of 24 months, the estimated 5-year overall and disease-free survival rates of the 63 patients was 31% and 29%, respectively. For the patients received HDT-HSCT as consolidation therapy, the 5-year OS rate was 59.8% compared with 18.0% for patients treated by CHOP-based regimens alone (p=0.0224). Bone marrow involvement, age ≥20 years, and primary refractory disease were factors significantly associated with poor outcome. Among the 18 patients with bone marrow involvement, only 3 patients that received allogeneic HSCT were still alive at the follow up time of 22, 32 and 37 months respectively.

Conclusions: LBL patients treated only with short term CHOP-based regimens are insufficient. Addition of HSCT as consolidation therapy and allogeneic HSCT could be treatment option for different patient subsets.

Key words: lymphoblastic lymphoma; CHOP regimen; stem cell transplantation

476 OBSERVATIONAL STUDY OF DIFFUSE LARGE B CELL LYMPHOMA PATIENTS WITH HIGHEST IPI RISK: PROGNOSIS AND THERAPEUTICS

A.E. Hallack Neto[1], F.L. Dulley[1], S.A. Siqueira[2], B. Beitler[1], M. Belesso[1], L.F. Pracchia[1], D.A. Chamone[1], J. Pereira[1]

[1]Haematology, University of São Paulo, São Paulo, Brazil, [2]Pathology, University of São Paulo, São Paulo, Brazil

Introduction: In order to improve the prognostic evaluation and the therapeutic approach to DLBCL patients with high intermediate to high age-adjusted IPI (aIPI), a research project was designed for the analysis of immunohistochemical markers and the role of autologous stem cell transplantation (ASCT) in first complete remission (CR) for this group of patients.

Material and methods: The impact of the expression of CD10, Bcl-6, MUM-1 and Bcl-2 markers on complete remission (CR), disease-free survival (DFS) and overall survival (OS), either individually and according to cell origin was evaluated by means of immunohistochemistry. Eighty-two patients aged under 60 years old were assessed, of which 16 (19.5%) underwent ASCT in first CR and were compared to patients receiving conventional chemotherapy and being monitored after CR.

Results: Immunohistochemistry was assessable in 73 cases, 24 (32.9%) being classified as GC-type and 49 (67.1%) as NGC-type, with no survival difference between the two groups. Bcl-2 expression was found in 37% (27) of the patients and was the single independent predicting factor of OS prognosis according to multivariate analysis. A significant tendency of expression of this protein was also observed for achieving CR, which was essential for longer survival, as shown by multivariate analysis. OS and DFS within 5 years were of 75% and 85.2% respectively for the group of 16 patients treated with ASCT, which resulted in lower relapse rates (6.5%) with statistically significant difference for DFS (p=0.015) when compared to the group of patients who achieved CR and was kept under monitoring.

Conclusions: In this study ASCT was found to be a safe procedure for improving survival rates of DLBCL patients with high intermediate to high aIPI risk. Also, the expression of Bcl-2 protein was found to be useful as one of the variables to be analysed in the therapeutic approach to these patients.

477 MORPHOIMMUNOLOGIC AND CLINICAL CHARACTERISTICS IN TREATMENT OF PATIENTS WITH DIFFUSE LARGE-CELL LYMPHOMA (DLCL) ASSOCIATED WITH HEPATITIS C VIRUS (HCV) INFECTION

S. Lepkov[1]

[1]*Therapy, Russian State Medical University, Moscow, Russian Federation, On Behalf of S.V.Lepkov, G.I.Storozhakov, R.S.Oscanova, V.M.Volynkina, S.D.Kosyura, I.V.Poddubnaya, L.G.Babicheva, A.M.Kovrigina, T.T.Kondratyeva, V.M.Sherstnev*

Background: Several studies have suggested an association between HCV and B-cell DLCL. Treatment and outcome of pts with DLCL and HCV infection are still a matter of debate.

Materials and Methods: analysis of clinical data and efficacy of treatment has been performed according to CHOP scheme including 25 pts with DLCL and HCV infection (group 1st) and 41 pts with DLCL without HCV infection (group 2nd). Median value of age of pts of the 1st and 2nd was 47 and 63 y.o., respectively. The prevent disease stages III and IV in the 1st and 2nd at a point of diagnosis was observed in 83% and 52% of pts, respectively, (P=0.02). LDH level was increased in 65% of pts of 1st and in 45% of pts of 2nd. Spleen damage in 1st was found in 65% of pts, and in 2nd - in 41% (P>0.05). ALT was above the norm in 88% of pts in 1st, and in 46% - in 2nd. In morphologic study plasma differentiation of tumor cells with significant of basophilia of cytoplasm cells were observed in 92% of pts in 1st and 2nd in 8% of pts. Morphoimmunologic study founded that in 92% of pts in 1st there was a positive reaction to proteins and RNA of HCV in tumor cells.

Results: Complete remission was reached in 64% of pts in 1st and in 76% - in 2nd (P>0.05). Median value of even free survival in 1st was 7 months, and in 2nd - 24 months (P>0.02). Recurrence in 1st was noted in 92% of pts, and in 2nd - in 37% of pts. Median value of total survival in 1st was 21 months, and in 2nd - 43 months (P>0.05). After taking courses of chemotherapy cytopenia of 3-4 stages in 1st was founded in 76% of pts, and in 26% - in 2nd. Hepatotoxicity in 1st was observed in 60% of pts, and in 2nd – in 12% of pts.

Conclusion: The study demonstrates: pts with HCV-associated DLCL differ from the patients with DLCL without HCV by clinical, morphoimmunologic of tumor, efficacy and tolerance of chemotherapy. It is required to conduct a specific research which would combine chemotherapy and antiviral therapy as well for these pts.