

# Aggressive lymphoma

## 320 PROGNOSTIC MODELS FOR OUTCOME PREDICTION IN NON-HODGKIN'S LYMPHOMAS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION: A MULTICENTER STUDY OF 1,123 PATIENTS ON BEHALF OF THE FONDAZIONE ITALIANA LINFOMI (FIL)

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**Introduction:** A precise prognostication of non-Hodgkin's lymphomas associated with hepatitis C virus (HCV) infection is not well established; particularly, the impact of liver toxicity after (immuno)-chemotherapy on the outcome of pts with HCV+ NHL is not fully clarified.

**Methods:** We analysed clinical and virological features, toxicity and prognosis of 1,123 pts with HCV+ NHL diagnosed from 1993 to 2010 in 15 Italian institutions.

**Results:** 555 cases were DLBCL, 551 indolent NHL (286 MZL) and 17 T-NHL; all pts were HIV-, 91% were HCV-RNA+ and 2.5% carried HBsAg. An (immuno)-chemotherapy regimen was administered as 1<sup>st</sup> line treatment in 922 pts (31% with reduced dose): 576 received a CHOP-like regimen (+ Rituximab in 271), 76 a III<sup>rd</sup> generation regimen, 187 alkylators, 30 purine analogues, 31 other regimens, 22 R alone. Overall, 357 pts received Rituximab. 37 pts with indolent NHL were treated with 1<sup>st</sup> line anti-HCV antiviral therapy, 14 of whom obtained both a complete virologic and haematological response. Overall, 100 out of 729 evaluable pts (14%; 15% of DLBCL and 12% of indolent NHL) developed severe hepatic toxicity (WHO grade 3-4), that lead to withdrawal of therapy in 29 pts. Use of Rituximab was not associated with increased rate of severe liver toxicity (p=0.5); particularly, in DLBCL R-CHOP and CHOP showed the same rate of severe hepatic toxicity (15%, p=ns). After a median F-U of 2.7 years, 348 pts died (24 for liver failure). 5-yr OS was 76% for indolent NHL and 62% for DLBCL. In DLBCL IPI and R-IPI were predictive of OS (p<0.001). Parameters associated with a shorter OS according to stepwise Cox regression analysis in indolent NHL and DLBCL are shown in Table 1. In indolent NHL, antiviral treatment either as 1<sup>st</sup> line and/or as subsequent therapy conferred a significant OS advantage (p=0.008). We combined the 3 factors significantly associated to a worse OS in DLBCL (ECOG, albumin, HCV-RNA load) in a new HCV Prognostic Score (HPS) able to discriminate 3 risk categories (low=0; intermediate=1; high risk ≥2 factors, p<0.001). After adjusting by IPI in multivariate Cox analysis, HPS retained prognostic effect (p<0.001), while IPI itself did not.

**Conclusions:** A significant proportion of pts with HCV+ NHL, when treated with conventional (immuno)-chemotherapy, develops severe liver toxicity. In indolent NHL, antiviral therapy at any time during lymphoma history ameliorates OS. In HCV+ DLBCL, the addition of rituximab to CHOP does not seem to increase hepatic toxicity; moreover, the new HPS score performs better than IPI in discriminating different risk categories.

Table 1 - Clinical parameters influencing OS in multivariate analysis.

	Prognostic factors	HR (95% CI)	p
INDOLENT NHL	Age >60	2.09 (1.10 - 3.94)	0.023
	ECOG ≥2	2.83 (1.37 - 5.83)	0.005
	AA stage III-IV	2.00 (1.03 - 3.87)	0.040
	No antiviral therapy at any time	3.46 (1.39 - 8.60)	0.008
DLBCL	ECOG ≥2	2.95 (1.53 - 5.67)	0.001
	Serum albumin <3.5 g/dl	2.58 (1.32 - 5.05)	0.006
	HCV-RNA >10 <sup>6</sup> UI/ml	2.98 (1.53 - 5.81)	0.001

## 321 ALBUMIN AND B2 MICROGLOBULIN IMPROVE IPI-BASED RISK STRATIFICATION IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA: AN ANALYSIS OF THE POPULATION-BASED DANISH LYMPHOMA REGISTRY, LYFO

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**Introduction:** The International Prognostic Index (IPI) is widely used for risk stratification of patients with diffuse large B-Cell lymphoma (DLBCL). Introduction of rituximab(R) has improved outcome, but not necessarily equal in all subgroups. Several studies have confirmed the IPI in the R era although extranodal involvement (EN) seems of less importance. Other studies have identified new factors that may have equal influence in a prognostic multivariate analysis (MVA).

**Material:** The Danish nationwide population-based Lymphoma Registry LYFO covers more than 95% of patients diagnosed and treated with malignant lymphoma. Clinical data at time of diagnosis, treatment regimen and relapse were registered. Information of death was drawn from national person registration, leaving no patients lost for survival analysis.

In the period 2000-2009 1884 patients with DLBCL treated with R-chemotherapy was extracted from LYFO. 1771 patients (94%) had all IPI factors (age, stage, EN, LDH and performance status) available for analysis.

**Results:** All IPI factors but extra-nodal involvement had an independent significance in the MVA. The sub-analysis of the 641 patients ages ≤ 60 years, gender had a borderline significance (p=0.05) with poorer overall survival (OS) in the male patients.

When beta2microglobulin was introduced in the model (with all IPI factors) a highly significant importance was seen. Also decreased albumin was of prognostic importance, whereas lymphocyte count was not and the stage was no longer of significant importance.

**Conclusion:** EN involvement is not of significant importance in the prognostic model. Albumin and beta2microglobulin should be included as prognostic markers in a revision of IPI, leaving out EN involvement and stage. Interestingly, a border significant difference in OS in benefit of female gender was found supporting the hypothesis that gender may be of importance, particularly in younger DLBCL patients.

## 322 PROPOSAL OF A MODIFIED PROGNOSTIC INDEX FOR ADULT BURKITT LYMPHOMA - A POPULATION BASED SWEDISH LYMPHOMA REGISTRY STUDY

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**Background:** Burkitt lymphoma (BL) is a rare neoplasm constituting 1-2% of adult B-cell lymphomas in the western world. Prognostic models and chemotherapy regimens have primarily been developed for the paediatric patient population and standard treatment for adult BL is still not defined. Our aims in this study were to establish prognostic factors for overall survival in adult BL and evaluate the efficacy of different chemotherapy regimens in a population based setting.

**Methods:** Our study population was collected from the Swedish Lymphoma Registry 2000-2010. During this period, 156 adult patients with BL were identified.

**Results:** Age and WHO performance status (PS) were statistically significant adverse prognostic factors for overall survival in multivariate analysis, and S-LDH was associated with adverse outcome in univariate analysis. In addition, there was a trend towards inferior overall survival in females (p=0.054).

A modified prognostic index, based on: age >40 years, PS >1, and LDH >ULN was proposed, separating the population in three distinct groups. Patients with a score of 0-1, 2 and 3 were found to have a 2-year survival of 91.2%, 58.4% and 27.5%, respectively.

High-intensity therapy regimens, i.e. BFM protocols or Hyper-CVAD were associated with more favourable outcome (2-year survival 80% and 78.6%), compared to patients receiving CHOP or other regimens (2-year survival 62.3% and 33%), although this could largely be explained as being due to differences in patient age.

Rituximab addition was not significantly associated with improvement in survival (HR=0.8, 95% C. I. 0.5-3.0).

**Conclusion:** Prognostic factors of importance for adult BL differ slightly from other aggressive lymphomas and a modified staging scheme may be valuable, as proposed. Further population based studies and/or randomised trials need to be performed to define standard treatment for adult BL.

### 323 OUTCOME OF LYMPHOMA DURING PREGNANCY: AN INDIVIDUALIZED THERAPEUTIC APPROACH RESULTS IN EXCELLENT PATIENT OUTCOMES AND MINIMAL OBSTETRIC OR FETAL COMPLICATIONS

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**Background:** Lymphoma complicating pregnancy is uncommon with a lack of data to guide the most optimal therapy.

**Methods:** A retrospective review was performed for patients (pts) diagnosed with Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL) during pregnancy from 1996-2010.

**Results:** 22 pts were identified with a median age of 31 years (22-40). 18% were diagnosed (dx) during the 1<sup>st</sup> trimester (Tri), 50% during 2<sup>nd</sup>, and 32% during the 3<sup>rd</sup> Tri. 55% had HL and 45% NHL (mostly aggressive NHLs); 36% of all pts had stage III/IV, 3 pts in the 1<sup>st</sup> Tri who needed immediate chemotherapy (Ctx), and 1 pt in the early 2<sup>nd</sup> Tri who warranted high-dose methotrexate, had their pregnancies terminated to enable treatment. Start of definitive therapy (besides intermittent steroids) was delayed until post-partum in 7 pts with stage I/II HL (5/7 diagnosed in 3<sup>rd</sup> Tri). 11 pts received non-anti-metabolite cytotoxic Ctx (n=10) or radiotherapy (RT) (n=1), which was initiated in the 2<sup>nd</sup> Tri in the majority (Table 1). Ctx was continued to allow a "near-term" delivery. Further, delivery was planned >3-4 weeks after the final intra-partum Ctx cycle. The overall response rate was 91% (CR 81%). Overall, pts delivered at a median of 37 wks (34-40) (induction of labor 39% and cesarean section rate 17%). Minimal complications occurred (pre-eclampsia and gestational diabetes 6% each; no chorioamnionitis). The mean birthweight of infants (n=18) was 2.8 Kg. None of the infants with available data (n=16) had any birth defects or developmental sequelae. With median follow-up of 36 months (12-137) for all pts, the 3-year PFS was 86% and 3-year OS rate of 95%.

**Conclusions:** Our report confirms that standard chemotherapy can be used safely during the 2<sup>nd</sup>/3<sup>rd</sup> Tri's and that an individualized therapeutic approach is associated with excellent maternal and fetal outcomes.

Table 1. Ctx received.

Dx	Gest. (wks)	Ctx started	Ctx
ALCL x 2	13, 32		Mod. hyperCVAD, Mod. ESHAP
DLBCL x 4	20, 22, 27, 29		R-CHOP
FL	22		R-CHOP
HL x 4	17, 17, 17, 24		ABVD x 2, AVD x 1, RT x 1 (respectively)

Gest, gestation; Mod, modified; ALCL, anaplastic large cell lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma.

### 324 REVIEW OF EBSTEIN BARR VIRUS (EBV) POSITIVE DIFFUSE LARGE B CELL LYMPHOMA (DLBCL) OCCURRING IN IMMUNOCOMPETENT PATIENTS IN THE WEST OF SCOTLAND

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**Introduction:** The WHO classification of tumours of haemopoietic and lymphoid tissue now recognise EBV positive DLBCL in immunocompetent patients as a distinct clinical entity. Although primarily a disease of the elderly it can occur in younger patients. The incidence, clinical behaviour and outcome of this entity in European countries has yet to be defined. We report on the pathological features and clinical outcomes of a series of patients from the West of Scotland (WoS).

**Methods:** Cases of EBV positive DLBCL in immunocompetent patients diagnosed between 2001 and 2009 were identified by searching a central pathology database. Clinical, morphological and immunophenotypic data were collated. Comparisons were made with a reference cohort of 120 consecutive patients diagnosed with DLBCL in WoS (population ~ 2.5 million) over a 2 year period.

**Results:** Twenty seven patients were identified, median age 66 years. Female: male, 2:1. Four patients were <40 years. Comparison with reference cohort showed similar numbers of patients with advanced stage and extranodal disease at presentation. There was a highly significant increase in disease of oral cavity and nasopharynx in the EBV positive group (43% vs 5%), p<0.001. Three morphological patterns were identified: DLBCL (n=10), plasmablastic (n=6) and Hodgkin-like (n=11). Sixteen cases had an activated B cell (ABC) immunophenotype, 3 cases germinal centre and 8 indeterminate. There was a significant excess of ABC phenotype in the EBV positive cases, p=0.001. CD30 was frequently positive (88% of cases). Nineteen patients were treated with CHOP or CHOP like anthracycline based therapy, 13 included rituximab. Seven received radiotherapy in addition. One patient had tumour resection only. The remaining patients received palliative treatment. Seven patients died within a year of diagnosis, 6 secondary to lymphoma and 1 from infection. Most of these cases were deemed unsuitable for chemotherapy due to comorbidities. Overall survival at 5 years was influenced by patient age (75% for <60yrs, 50% for >60yrs) and treatment (CHOP/CHOP like 64.4%, other 37.5%). There was a trend toward improved overall survival in the EBV+ DLBC group, p=0.058.

**Conclusion:** EBV positive DLBCL of the elderly has a wide morphological spectrum and frequently affects the upper aerodigestive tract. Previously thought of as a disease with poor prognosis, we have demonstrated that patients with this entity in the West of Scotland have a similar outcome to EBV negative DLBCL.

### 325 HEMATOLOGICAL AND VIROLOGICAL FEATURES OF NON-HODGKIN'S LYMPHOMAS ASSOCIATED WITH HEPATITIS C VIRUS INFECTION: A PROSPECTIVE OBSERVATIONAL STUDY ON BEHALF OF THE RETE EMATOLOGICA LOMBARDA (REL)

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**Introduction:** The association between hepatitis C virus (HCV) infection and non-Hodgkin's lymphomas (NHL) has been demonstrated in epidemiological studies. HCV infection is still a public health problem; in Lombardia, a densely populated region of northern Italy with around 10 millions of inhabitants, the prevalence of infected people is around 5%. In order to study the features of HCV-related NHL, we pursue a prospective multicentric observational study in Lombardia. We present here the characteristics and evolution of the patients (pts) included in this study.

**Methods:** Since January 2008 we collected histological, clinical and therapeutic data of 218 consecutive pts with NHL and HCV infection, diagnosed in Hematology Centres of the "Rete Ematologica Lombarda" (Lombardy Hematology Network). This prospective observational study (Registro Lombardo dei Linfomi HCV-positivi) was approved by the Regional Administration and by IRBs of participating institutions. All pts signed a written informed consent.

**Results:** Males/females ratio was 87/131; median age at diagnosis was 68 yrs (range 36-84). Histotypes were: 99 DLBCL, 57 MZL (19 splenic, 13 nodal, 25 extranodal of MALT), 22 follicular lymphoma, 6 small lymphocytic lymphoma, 6 lymphoplasmocytic lymphoma, 2 mantle cell lymphoma, 26 low-grade B-cell lymphoma NOS. Ann Arbor stage was III-IV in 171, with bone marrow involvement in 96; ECOG score was ≥ 2 in 34. 133 pts showed at least one extranodal localization (spleen in 42, skin in 25, Waldeyer's ring in 10, ocular adnexa in 8). Virological data are summarized in Table 1. Presence of serum MC (p=0.003), autoimmunity (p<0.001), cryoglobulinemia (p=0.005) were statistically associated with indolent NHL. 144 pts had a known HCV-positivity before the diagnosis of NHL and 40 pts (28%) were treated with antiviral therapy. Data on treatment were available in 201 pts. 151 pts received chemotherapy (in 97 with Rituximab). A grade 3-4 WHO liver toxicity developed in 12 pts and 5 pts interrupted the treatment. Pts with liver toxicity and/or drug reduction of dosage and/or early interruption of therapy showed a worse OS (p=0.01) and PFS (p=0.03).

**Conclusions:** In this prospective collection of data within a regional hematology network most frequently reported histologies are DLBCL and MZL. In a significant proportion of indolent and aggressive lymphoma pts, first detection of HCV infection is concurrent to lymphoma diagnosis. HCV infection seems to hamper, in a significant subset of cases, full dose administration of (immuno)-chemotherapy.

Table 1 - Virological data of 218 patients with non-Hodgkin's lymphoma associated with HCV infection.

	Aggressive lymphomas	Indolent lymphomas
Detection of HCV	99	119
- previous NHL diagnosis	70/99	74/119
- concurrent NHL diagnosis	29/99	45/119
Child-Pugh Score*	22/97	11/118
- A	12/17	6/9
- B	5/17	3/9
Liver histology	16	23
- lymphoma involvement	5/16	11/23
- chronic hepatitis	14/16	15/23
HCV-RNA+*	67/73	92/100
- genotype 1	16	26
- genotype 2	12	45
- genotype 3	1	3
- genotype 4,5,6	3	0
HBV co-infection status*	92	108
- HbsAg+/HBV-DNA-	6/92	3/108
- HbcAb+	36/79	32/92

\* at diagnosis of NHL

### 326 IMPROVED SURVIVAL ASSOCIATED WITH INCREASED BODY MASS INDEX (BMI) IN DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)

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**Introduction:** Previous studies have demonstrated a positive relationship between BMI and risk of death from non-Hodgkin lymphoma (NHL). It remains unclear if obesity causes an increase in NHL incidence, increased mortality after NHL diagnosis, or both. Using a retrospective cohort of DLBCL patients in the United States Veterans Health Administration (VHA) database, we evaluated the influence of BMI at the time of diagnosis on overall survival (OS). To our knowledge, this represents the largest cohort of patients with DLBCL not treated in a clinical trial in whom the relationship between BMI and OS has been evaluated, and the only one with data from the post-rituximab era.

**Methods:** Records of patients diagnosed with DLBCL between October 1998 and September 2008 were identified in the VHA cancer registry. Data was obtained on patient demographics, date of diagnosis, stage, co-morbidities, height, weight, and International Prognostic Index (IPI). Co-morbidities were converted into a single score using the Charlson index. Of 3,052 HIV negative patients, 2,455 patients (80%) had complete information, with the exception of IPI. IPI was available on a subset of 507 patients (21%).

**Results:** Mean patient age was 67.4 years, 97% were men, with 26%, 17%, 20% and 38% stages I, II, III, and IV, respectively. Cox modeling evaluated the impact of BMI on OS, controlling for age, stage, Charlson score, and year of diagnosis (an indirect measure of rituximab use). Compared to normal weight patients (BMI 18.5 to <25), underweight patients (BMI <18.5) had worse OS (HR 1.411, p=0.012), while overweight (BMI 25 to <30) and obese (BMI ≥ 30) patients had improved OS (HR = 0.709, p< 0.0001 and HR= 0.663, p< 0.0001, respectively). Older age, advanced stage, higher Charlson score, and earlier year of diagnosis were all associated with worse OS. In patients with IPI data, only underweight patients had a significant difference in baseline IPI compared to patients with normal BMI (mean = 3.14 vs. 2.23, p = 0.019). A similar relationship between BMI and OS was observed in both the pre- and post-rituximab eras.

**Conclusions:** BMI in the overweight or obese range at time of DLBCL diagnosis was associated with significantly better OS, both pre- and post-rituximab. Possible reasons for the better prognosis in overweight and obese patients include: Better prognosis DLBCL phenotype, improved chemotherapy tolerance, or improved physiologic reserve. Understanding the reasons for the difference in prognosis may improve the understanding of the pathophysiology and/or treatment of DLBCL disease in obese and non-obese patients.

### 327 ADDITION OF LOW-DOSE, INVOLVED-FIELD EXTERNAL BEAM RADIOTHERAPY JUST PRIOR TO RADIOIMMUNOTHERAPY FOR B-CELL LYMPHOMA: "PRIMING" CELL DEATH PATHWAYS

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**Introduction:** Radioimmunotherapy is an effective and increasingly used option for patients with B-cell lymphomas. Particularly in the relapsed/refractory setting, patients may have sizable disease limited to one or a few sites. Many patients are heavily

pretreated, with a subsequent downregulation of CD20 expression on the surface of lymphoma cells. Emerging evidence suggests a role for stressors (such as low-dose local irradiation) to upregulate CD20 expression and to stimulate cellular death pathways. These changes could potentially sensitize the irradiated lymphoma cells to radioimmunotherapy.

**Methods:** Between July 1, 2009, and December 31, 2010, we treated 13 patients with a combination of low-dose, involved-field radiotherapy (IFRT) and radioimmunotherapy (RIT) for relapsed/refractory B-cell lymphoma: 5 transformed, 4 follicular, 2 marginal zone, 1 CLL/SLL, and 1 lymphoplasmacytic. All received 4 Gy in 2 fractions IFRT to sites of active disease, 2.5 cm or larger. <sup>131</sup>I-tositumomab was used in 8 patients and <sup>90</sup>Y-ibritumomab tiuxetan in 5 patients. In all cases, IFRT was delivered between the dosimetric and therapeutic doses of RIT, on non-consecutive days. The median age of patients treated was 61 (38 – 82). The median number of prior therapies was 2 (1 – 4). The median size of persistent disease prior to treatment was 4.2 cm (2.5 – 19.5).

**Results:** With a median follow-up of 14 months (6 – 21), 11/13 patients obtained a complete response to combined therapy and remain in remission at this time. No patients have failed within the IFRT fields. Two patients achieved a local CR but exhibited persistent disease outside the IFRT fields. Both of these patients underwent bone marrow transplant and died from complications of this therapy. All 13 patients tolerated combined IFRT and RIT very well with no toxicity from the addition of IFRT, and only transient grade 2-3 hematologic toxicity from the RIT. The progression-free survival (PFS) is 100% in patients achieving a CR and is 85% for all patients treated.

**Conclusion:** The addition of IFRT to sites of active disease ≥ 2.5 cm to RIT in patients with relapsed/refractory B-cell lymphomas is well-tolerated, adds no toxicity to that of RIT alone, and results in excellent PFS, particularly for patients who obtain a CR. As the only failures to therapy were outside of radiation portals, the addition of IFRT to sites of active disease may play an important role in improving PFS when added to RIT. Prospective studies are needed to further evaluate this novel combined therapeutic approach. Correlative studies should be pursued to determine the mechanism of this improved tumor control.

### 328 TEN YEARS RELATIVE SURVIVAL ANALYSIS OF THE GELA-LNH985: THE FIRST RANDOMIZED STUDY COMPARING RITUXIMAB-CHOP TO STANDARD CHOP CHEMOTHERAPY IN DLBCL PATIENTS

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**Background:** In patients with diffuse large B-cell lymphoma (DLBCL), deaths during the first 2 years mostly reflect treatment failure or relapse. In the other hand, delayed deaths could be due to the return of the underlying mortality hazard (e.g. age-associated morbidity). We aimed to analyze the 10 year outcome of patients included in the LNH98-5 study comparing CHOP to CHOP plus rituximab (R-CHOP) by focusing on the relative survival (RS). This new epidemiological approach compares the observed survival in the study population with the expected survival in the general population.

**Patients and Methods:** LNH98-5 was a randomized study that included 399 previously untreated patients, aged 60 to 80 years, with diffuse large B-cell lymphoma. Patients received 8 cycles of classical CHOP (cyclophosphamide 750 mg/m<sup>2</sup>, doxorubicin 50 mg/m<sup>2</sup>, vincristine 1.4 mg/m<sup>2</sup>, and prednisone 40 mg/m<sup>2</sup> x 5 days) every 3 weeks. In R-CHOP, rituximab was given the same day of CHOP at the dose of 375 mg/m<sup>2</sup>. Follow up data was updated in July 2009. The RS probabilities were estimated using the mortality rates published by INSEE [http://www.insee.fr/]. RS are computed as the ratio between overall survival (OS) in the study population and the expected survival in the general population matched for age and gender.

**Results:** Overall, the 10-yr OS rate was 35% and the 10-yr RS rate was 48%. Since there was a treatment effect of R-CHOP on 10-yr OS (44 vs 28%, P = 0.004), its impact was tested in term of RS. The difference between R-CHOP and CHOP in 10-yr RS was also significant (56 vs 38%, P = 0.0013).

More patients died from causes unrelated to lymphoma or its treatment in the R-CHOP arm: cancer (9% in both arms) and other diseases (21 and 11%, respectively) mainly cardiovascular diseases (16 vs 10%, respectively) but no pattern emerged, as most of the underlying conditions related to the death were present before the diagnosis of DLBCL.

Lastly, the annual relative mortality rate was estimated at 1% after the fifth years in patients receiving R-CHOP.

**Conclusion:** Combination of rituximab plus CHOP allows a large improvement of the 10-yrRS in elderly patients. However, there remains an excess of mortality when compared with the general population. In long-term survivors, we recommend a secondary prophylaxis for the well-known risks factors of cancer and cardiovascular diseases.

### 329 7-YEAR FOLLOW-UP OF THE RICOVER-60 TRIAL OF THE GERMAN HIGH-GRADE NON-HODGKIN LYMPHOMA STUDY GROUP (DSHNHL)

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**Background:** Interval reduction from 3 (CHOP-21) to 2 weeks (CHOP-14; Pfreundschuh *et al.*, *Blood*, 2004) and the addition of rituximab to CHOP-21 (R-CHOP-21; Coiffier *et al.*, *NEJM*, 2002) improved outcome in elderly patients with DLBCL to a similar extent compared to CHOP-21.

**Methods:** In the RICOVER-60 trial, elderly patients (61-80 years) were randomized to receive 6 or 8 cycles of CHOP-14 with or without 8 cycles rituximab. Radiotherapy was planned to sites of initial bulk and/or extranodal involvement. The primary endpoint was event-free survival (EFS), secondary endpoints were progression-free survival (PFS) and overall survival (OS).

**Results:** Between 07/2000 and 06/2005, 1222 patients with CD20<sup>+</sup> aggressive B-cell lymphoma were recruited and are evaluable (median age 68 years; IPI=1: 30%, IPI=2: 28%, IPI=3: 26%, IPI=4,5: 16%). There was no difference between the four arms with respect to long-term toxicity and second neoplasms. As by intention to treat, the 7-year EFS rate was 33% after 6xCHOP-14 (n=307), 40% after 8xCHOP-14 (n=305), 50% after 6xR-CHOP-14 (n=306), and 52% after 8xR-CHOP-14 (n=306). After a median observation time of 82 months, the estimated 7-year overall survival (OS) rates were 50% for 6xCHOP-14, 52% for 8xCHOP-14, 62% for 6xR-CHOP-14, and 60% for 8xR-CHOP-14. In a multivariate analysis using 6xR-CHOP-14 without rituximab as the reference and adjusting for the stratification variables elevated LDH, advanced stage III&IV, ECOG performance state >1, bulky disease, >1 extranodal site, and age >70, both rituximab arms had a significantly improved EFS (6xR-CHOP-14: RR=0.5, p<0.001; 8xR-CHOP-14: RR=0.5, p<0.001), PFS (6xR-CHOP-14: RR=0.5, p<0.001; 8xR-CHOP-14: RR=0.5, p<0.001) and OS (6xR-CHOP-14: RR=0.6; p<0.001; 8xR-CHOP-14: RR=0.7; p=0.004).

**Conclusions:** In contrast to the 3-year follow-up, not only 6xR-CHOP-14, but also 8xR-CHOP-14 achieved a significantly better overall survival compared to 6xCHOP-14 after a median observation time of 82 months. With respect to all endpoints, 6xR-CHOP-14 was slightly, but not significantly better than 8xR-CHOP-14. Therefore, due to its lower toxicity and shorter time under chemotherapy (6xCHOP-14: 10 weeks, 8xCHOP-14: 15 weeks, and 8x-CHOP-21 even 21 weeks plus 1 day), 6xCHOP-14 in combination with 8 applications of rituximab is the preferred regimen for elderly patients with CD20<sup>+</sup> aggressive lymphomas. Supported by Deutsche Krebshilfe.

### 330 TREATMENT DESCALATION BASED ON EARLY FDGPET IN PATIENTS WITH POOR RISK DIFFUSE LARGE B CELL LYMPHOMA (DLBCL). A PROSPECTIVE PHASE II GELTAMO TRIAL

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**Background:** Rituximab has improved prognosis in DLBCL, however OS for high IPI patients is only 58%. In order to improve outcome, ASCT is still considered in some prospective trials. The aim of our study is to assess the role of early PET to deescalate treatment and avoid transplant in patients PET negative after 3 courses.

**Patients and Methods:** A prospective non-randomised phase II trial (EudraCT: 2006-005254-68) was undertaken in 20 centers. Primary endpoint was progression-free-survival (PFS). Only aIPI>1 or 1 with a High beta 2 were included. All patients received 3 R-MegaCHOP. A PET scan was performed at diagnosis and after the third cycle; Pts with PET - received 3 more R-MegaCHOP cycles; Pts with PET+ received early salvage therapy with 2 R-IFE cycles and those in PR or CR underwent ASCT with BEAM.

**Results:** A total of 73 pts were included. Median age was 54 years (25-65). 66 pts were evaluated after 3 cycles of R-MegaCHOP: 54.5% achieved CR (PET -) and received 3 more R-MegaCHOP without transplant; 0.7 % progressed; 44.9% (PET +) received R-IFE and ASCT. 91.6% of the early PET - group completed 6 cycles of chemotherapy and 89.6% of the early PET + group received the R-IFE

and ASCT. A median follow-up of 19 months, 3-year PFS and OS in an intention to treat analysis were 68% and 77% respectively. 3-year PFS and OS were 79% and 87% in the R-MegaCHOP (6 relapses, 4 deaths), and 59% and 73% in the R-IFE/ASCT arm (6 progressions, 6 deaths) (p>0.1 in both groups).

**Comments:** Our preliminary results show that, in patients with unfavourable DLBCL, good results could be obtained after induction with R-MEGAChOP with or without ASCT; a treatment deescalation based on early PET could be an option, with ASCT only for patients with a slower response.

### 331 LENALIDOMIDE PLUS RITUXIMAB-CHOP21 IN ELDERLY UNTREATED DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL): RESULTS OF PHASE I PART OF REAL07 TRIAL OF ITALIAN LYMPHOMA FOUNDATION (FIL)

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**Background:** RCHOP is the standard in elderly DLBCL, however 30-40% patients failed. Lenalidomide (L) in relapsed/refractory DLBCL is promising. On these basis, FIL is running a prospective multicenter dose finding phase I-II trial to evaluate toxicity and efficacy of L plus RCHOP21 (LRCHOP) for elderly untreated DLBCL (NCT00907348). Aim of the phase I was to define Dose Limiting Toxicity (DLT), maximum dose inducing any grade >2 non-hematologic toxicity, or a >15 days delay of planned cycle.

**Patients and Methods:** Inclusion criteria were: age 60-80; untreated DLBCL; Ann Arbor stage II,III,IV; IPI at low-intermediate/intermediate-high/high (LI/IH/H) risk. Treatment plan was: 6 RCHOP21 in association with L days 1-14 at the established dose level. Phase I was planned to define the Maximum Tolerated Dose (MTD) that is the dose that achieves a DLT in 33% or less patients; evaluation was planned after 3 LRCHOP. Study was designed with the Continual Reassessment Method (CRM), a Bayesian memory design that uses, as dose allocation rule of the sequentially incoming patients, the re-estimated probability of toxicity based on the results obtained for the patients already observed. Four doses of L were tested: 5, 10, 15 and 20 mg. At the end of each cohort, the dose level associated with an updated DLT probability closest to 33% was recommended to be administered to the next cohort.

**Results:** From May 2008 to February 2010, 21 patients were enrolled. Clinical characteristics were: median age 68 (61-77); stage III/IV 81%; PS>1 81%; IH/H IPI 52/24%. Patient allocation by L was: 5 mg in nobody, 10 mg in 9, 15 mg in 9 and 20 mg in 3. DLTs in the first 3 LRCHOP were recorded in 7 patients; according to CRM, these events determined L 15 mg/die as the MTD. Of 115 LRCHOP courses, hematological toxicity was mild: grade III/IV thrombocytopenia 10%, anemia 4% and neutropenia 28%. Extra-hematological toxicities were moderate: grade IV increase of CPK in one patient, grade III cardiac in one, grade III neurological in 3 and grade III infections in 4 (two pneumonias, one febrile neutropenia with diarrhea and one diarrhea). At the end of 6 LRCHOP, complete remission was achieved in 76% patients.

**Conclusions:** MTD for LRCHOP is L 15 mg. LRCHOP is safe and feasible in elderly DLBCL, with promising preliminary efficacy results. The ongoing phase II part of the trial is aimed to test the efficacy of 15 mg of L in association with RCHOP21.

### 332 DOSE ADJUSTED INFUSIONAL CHEMOTHERAPY WITH/WITHOUT RITUXIMAB (DA EPOCH +/- R) IN AGGRESSIVE NON-HODGKIN'S LYMPHOMA (NHL): THE IRISH EXPERIENCE

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**Background:** DA EPOCH+/-R chemotherapy is an infusional regimen that incorporates a dynamic dose adjustment strategy based on haematopoietic nadirs. It is a rationally designed regimen to overcome chemoresistance with use of non-crossresistant drugs and maximizes dose intensity. While initially designed in the National Cancer Institute, Maryland, USA, a CALGB phase III randomized trial is currently recruiting. We present the experience in Ireland of its use in aggressive non-Hodgkin's lymphoma.

**Methods:** This was a multi-institutional retrospective study of patients with aggressive NHL receiving dose adjusted EPOCH+/-R. Patient demographics, pathology, stage,

International Prognostic Index (IPI), dose intensity, toxicity, response and outcomes were assessed.

**Results:** Sixty two patients treated with DA EPOCH+/-R were identified. Of those, 41 (66%) were male. The median age was 53 (range 17-87) years. Only 2 patients received this regimen in the relapsed setting. The majority (73 %) of patients had diffuse large B cell lymphoma, while other diagnoses included primary mediastinal B cell lymphoma, transformed lymphoma, Burkitt's lymphoma, and Plasmablastic lymphoma. Seventy percent of patients had stage IIB or higher disease; in fact 49% had stage IV disease. Twenty seven patients (44%) had an IPI of three or more. A median of 6 (range 1-6) cycles were administered. In total, 312 cycles were administered; dose intensity was achieved in 77% of cycles. Fifty-nine patients were evaluable for response. 73% of patients achieved CR and 14% PR. Of those with a low IPI score ( $\leq 2$ ), 88% responded. In the high IPI group ( $> 2$ ), 77% responded. 65% of cycles resulted in grade 3/4 haematological toxicity. Grade 3/4 non-hematological toxicity was seen in 9% of cycles.

**Conclusion:** While we eagerly await the results of the CALGB study, we demonstrate that DA EPOCH +/-R may be administered safely outside of clinical trials, with reproducible outcomes and acceptable toxicity.

### 333 ALTERNATING HIGH-DOSE METHOTREXATE WITHIN R-CHOP21 IS FEASIBLE IN AGGRESSIVE B-CELL LYMPHOMA PATIENTS AT RISK FOR CNS INVOLVEMENT

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**Introduction:** About 5% of patients with aggressive B-cell Non-Hodgkin's lymphoma experience CNS involvement at relapse. Elevated LDH, involvement of more than one extranodal site and a high International Prognostic Index (IPI) are among the factors considered to increase the individual risk to over 20%. We therefore added high-dose MTX (HD-MTX) to standard treatment in patients with B-cell Lymphoma with high risk for CNS disease.

**Material and Methods:** Between April 2009 and January 2011, 9 patients with B-cell lymphoma (6 diffuse large B-cell lymphoma, 1 primary mediastinal B-cell lymphoma, 1 follicular lymphoma grade 1-2, and 1 follicular lymphoma grade 3A) with a median age of 57 years (range, 20 - 72) presented with involvement of more than one extranodal site in 7 cases, and paravertebral lesions with contact to the meningeal sack in 2 cases. Moreover, IPI  $\geq 4$  and elevated LDH were present in 5 and 6 patients, respectively. HD-MTX cycles were interspersed 14 days after R-CHOP cycles. Ideally, the following scheme was adopted: d1 = R-CHOP, d15 = HD-MTX, d22 = R-CHOP, d36 = HD-MTX, d43 = R-CHOP, and so on. HD-MTX was given at 4 g/m<sup>2</sup> as 4 hour infusion with intensive hydration and standard folinic acid rescue.

**Results:** Overall, a total of 52 R-CHOP and 27 HD-MTX cycles (1 patient is still undergoing treatment) were administered with a median of 3 HD-MTX cycles (range, 2-4) for each patient. The median interval between 2 R-CHOP cycles encompassing a HD-MTX cycle was 22 days (range, 20 - 38). The treatment was well tolerated without significant toxicity. One week after the HD-MTX cycles, i.e. immediately before the following R-CHOP cycles, median white blood cell and platelet counts were 4,4 x 10<sup>9</sup>/L (range, 1,6 - 9,7) and 245 x 10<sup>9</sup>/L (range, 89 - 569), respectively. Leukocytopenia and thrombocytopenia of any grade due to HD-MTX occurred in 21% and 0%, respectively. None of the patients suffered renal toxicity. Disappointingly, two relapses occurred 2 and 10 weeks after completion of treatment.

**Conclusions:** Although small, this study shows that intercalating standard R-CHOP treatment with 2 to 4 cycles of HD-MTX is feasible without disrupting dose density of the R-CHOP21 scheme and without adding significant toxicity. However, CNS relapses occurred, suggesting that this approach may not be sufficient to prevent CNS disease in all patients. A larger study in selected high-risk patients is now justified in order to clarify whether a reduction of CNS involvement can be achieved by adding HD-MTX to R-CHOP.

### 334 EARLY DEATH IN PATIENTS DIAGNOSED WITH NON-HODGKIN'S LYMPHOMA

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**Introduction:** Non-Hodgkin's lymphoma (NHL) is known to be sensitive to chemotherapy and/or irradiation. Albeit this early death still occurs in patients shortly after the diagnosis of NHL. The aim of the present study was to review the characteristics of patients who died within 4 months from diagnosis of NHL.

**Methods:** We retrospectively reviewed all adult NHL cases presenting to our center since 1985 that had died within 4 months from NHL diagnosis. Information on patient age, gender, date of diagnosis and date of death, cause of death, histology, lymphoma grade, stage, Ki-67 proliferation index, occurrence

of B symptoms, bulky disease, LVEF, performance status, Lactic dehydrogenase (LDH) levels, Serum  $\beta 2$ -microglobulin ( $\beta 2$ -M) level, IPI risk, treatment, and occurrence of serosal effusions were retrieved from the hospital databases.

**Results:** 94 patients were identified. They consisted 7% of our patient registry. The mean overall survival was 1.9 months, median 1.2 months. The mean age was 74 years (range 40-93 years). There were 40 males and 52 females. 79 patients (86%) had B cell NHL and 12 (13%) had T cell NHL. The most frequent pathologic classification was diffuse large B-cell lymphoma diagnosed in 69 patients (75%). 5 patients (5.5%) had indolent NHL, 83 (90%) aggressive NHL and 2 (2%) very aggressive NHL. Stage I disease was recorded in 8.5%, II in 7.5%, III in 11%, and IV in 73%. Bulky disease was recorded in 66%. Extranodal lymphoma was present in 79 patients (86%) and 49% had  $\geq 2$  extranodal sites. High PS (2-4) was found in 76% and high IPI in (3-5) in 89%. The mean Ki-67 proliferation index measured in 44 patients was 71%, B symptoms in 84%, elevated LDH in 80%.  $\beta 2$ -M level were elevated in 89% and the mean value was 4.69 mg/L. Serosal effusion mainly pleural effusion was present in 47%. Previous cancer was documented in 20 patients (22%). 19 patients received no treatment and 10 received only steroids. Chemotherapy was administered to 54 patients (59%) most of them CHOP regimen or alike.

**Conclusions:** Early death occurs in at least 7% of newly diagnosed NHL patients. Those are usually elderly patients with aggressive lymphoma, poor PS, advanced stage, extranodal disease, B symptoms, bulky disease, and elevated LDH and  $\beta 2$ -M and with serosal effusion. These early deaths resulted from sepsis, severe underlying disease, disease progression or gastrointestinal perforation. The selection of appropriate treatment modalities for these patients is a real challenge. They should undergo comprehensive geriatric assessment and receive individualized tailored treatments with protocol adjustment to their condition, strict clinical surveillance, best supportive care and maybe, as recently suggested, a prephase treatment.

### 335 MULTICENTER ANALYSIS OF 300+ VERY ELDERLY NON-HODGKIN LYMPHOMA (NHL) PATIENTS ( $\geq 80$ YEARS): IMPACT OF CO-MORBIDITIES AND FUNCTIONAL STATUS ON OUTCOME

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**Background:** The incidence of NHL rises exponentially with age and this is the most rapidly growing segment of society. Further, patients (pts)  $>$  age 80 years are underrepresented in clinical trials and data on their disease characteristics and outcome is sparse.

**Methods:** A multicenter retrospective review of pts  $\geq 80$  with an initial diagnosis of NHL (1999 - 2009) was completed. Co-morbidities were scored using the Cumulative Illness Rating Scale for Geriatrics (CIRS-G). Presence of geriatric syndromes at initial diagnosis (dx) were collected along with activity of daily livings (ADLs).

**Results:** 303 pts were identified [170 aggressive (143 B-cell), 133 indolent (109 B-cell)]. DLBCL was the most common (74%) aggressive (Agg) NHL. Follicular NHL was the most common (25%) indolent (Ind) histology. Median age was 83.5 (80-95) with 45% males, stage III/IV in 52%, high LDH in 39%, and reduced renal function in 23%. Notably, 31% of pts had prior malignancy, the majority of which had prior radiation. Only 6% had  $>$  1 extranodal site and 11% had bulky disease ( $>$  5 cm). In terms of geriatric assessments,  $\geq 1$  geriatric syndrome was present in 26% (dementia most common: 25%), non-fit classification in 30%, while 14% had loss of ADLs. Further, 18% of pts had a grade 4 CIRS-G in at least 1 category. Pts with Agg B-cell received rituximab (R) based therapy in 66%; 40% had dose reductions/delays, despite use of growth factors in 68%. For Ind B-cell pts, 39% were 'observed' for a median of 26 months; when treated (Tx), 44 received a R-based regimen. Collectively in Agg NHL, the overall response rate (ORR) was 65% (44% CR), while when Tx, the ORR for Ind NHL was 60% (32% CR). At 49-month median follow-up (6-149), 4-year progression-free survival (PFS) and overall survival (OS) for Agg NHLs were 31% and 44%, respectively (stage I/II: PFS 53%, OS 66% vs stage III/IV: PFS 20%, OS 32%;  $p < 0.0001$  and 0.0002, respectively). 4-year PFS and OS for all Ind NHLs were 44% and 66%, respectively, with no survival differences noted between stages. Additionally, no differences in PFS or OS were seen comparing CLL vs CTCL vs other Ind NHL histologies. Prognostic factors were identified (Table). Multivariate cox regression for Agg NHL showed that stage III/IV, ADL loss, and  $<$  CR correlated with PFS and OS, while the latter 2 were significant factors for Ind NHL.

**Conclusions:** Geriatric assessment tools, including CIRS and ADLs, are powerful predictors of outcome and complement more standard prognostic features. Incorporation of geriatric prognostic models should be prospectively studied.

Table. Prognostic factors (univariate).

Prognostic factors	Agg NHL (n=162)			
	PFS		OS	
	HR*	p	HR*	p
PS 2-4	1.69	.01	2.35	.0003
▲LDH	1.55	.03	1.68	.02
▼Albumin		NS	1.35	.0003
Stage III/IV	2.40	.0001	2.49	.0003
BM involved	1.93	.005	1.60	.06
IPI 3-5	1.91	.002	2.26	.005
No CR to initial Tx	2.88	<.0001	2.35	.0002
Loss of ADLs	2.89	<.0001	3.87	<.0001
Any CIRS 4		NS	1.99	.004
Any geriatric synd		NS	1.77	.007

  

Prognostic factors	Ind NHL (n=126)			
	PFS		OS	
	HR*	p	HR*	p
B symptoms		NS	2.11	.05
Weight loss >10%		NS	2.81	.003
No CR to initial Tx	2.19	.01	2.91	.006
Loss of ADLs	3.58	.002	5.56	.0002
Any Geriatric synd	1.86	.01	1.69	.05

Abbreviations: HR, hazard ratio; synd, syndrome; tx, treatment; NS, not significant.

\*HRs >1 indicate increased risk of progression and/or death.

### 336 PROGNOSTIC IMPACT FOR DIFFERENT SITES OF EXTRANODAL INVOLVEMENT IN PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA IN THE RITUXIMAB ERA

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**Introduction/Background:** Extranodal involvement is considered poor prognostic factor for patients with diffuse large B-cell lymphoma (DLBCL); however, the prognostic impact of each involvement site has not yet been fully elucidated.

**Material and methods:** We retrospectively analyzed data for 1,221 patients uniformly treated by standard R-CHOP therapy between 2003 and 2006. We evaluated 26 extranodal involvement sites (orbita, nasal cavity, paranasal sinus, Waldeyer ring, salivary gland, thyroid gland, breast, thymus, lungs, pleura, stomach, small intestine, colon, peritoneum, liver, pancreas, kidney, spleen, adrenal gland, testes, ovary/uterus, bones, bone marrow, peripheral blood, skin, and subcutaneous tissue) with respect to prognostic impact.

**Results:** The median age was 64 years (range, 15–91 years). Univariate analysis revealed that the patients with certain extranodal involvement had significantly worse overall survival (OS) than did the patients without the extranodal involvement; these sites included nasal cavity, paranasal sinus, lungs, pleura, small intestine, peritoneum, liver, pancreas, stomach, spleen, adrenal gland, testes, bones, bone marrow, peripheral blood, skin, and subcutaneous tissue. Patients with Waldeyer ring involvement had significantly better OS. Multivariate analysis revealed that patients with involvement of pleura (P < 0.001), small intestine (P = 0.015), peritoneum (P = 0.002), adrenal gland (P < 0.001), testes (P = 0.005), bone marrow (P < 0.001), and peripheral blood (P = 0.002) had significantly worse, but Waldeyer ring had significantly better OS (P = 0.038).

**Conclusions:** Extranodal involvement affects the prognosis of patients undergoing R-CHOP therapy for DLBCL. Waldeyer ring involvement may be a better prognosis factor.

### 337 IMPACT OF RITUXIMAB ON OUTCOMES OF VERY ELDERLY PATIENTS WITH DIFFUSE LARGE B-CELL LYMPHOMA

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**Background:** Randomized trials have shown that the addition of rituximab to cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) chemotherapy improves the survival of patients (pts) with diffuse large B-cell lymphoma (DLBCL). However, very elderly pts (i.e. aged  $\geq 80$  years) were excluded from these trials. Thus, the magnitude of benefit and the toxicity associated with the addition of rituximab in this population is unknown. We conducted a multi-institutional phase IV analysis of the survival and toxicity associated with addition of rituximab to chemotherapy for pts with DLBCL, including those aged  $\geq 80$  at time of diagnosis.

**Methods:** Using population-based registries in Ontario, we identified 4,021 pts who received chemotherapy with or without rituximab (R-CHOP or CHOP) for the primary treatment of DLBCL from 1996–2007, including 397 pts aged  $\geq 80$ . After hard-matching based on age and subsequent propensity score matching on gender, comorbidity, and treatment modality, the overall survival (OS) and toxicity (based on 1-year hospitalization rates) for those receiving R-CHOP were compared with pts treated with CHOP. A subgroup analysis was performed for very elderly pts.

**Results:** After matching, there were 1,131 pts in each of the R-CHOP and CHOP treatment groups, with a median follow up of 3.6 and 9.7 years, respectively. R-CHOP was associated with significant improvement in 5-year OS compared to CHOP (62% vs. 54%, p<0.001). For pts aged  $\geq 80$  at diagnosis, the addition of rituximab improved OS rates at 3-years (47 vs 30%, p=0.07) and at 5-years (32% vs. 25%, p = 0.07). Pts treated with R-CHOP had a higher 1-year rate of hospital admission for angina (1.3% vs. 0.4%, p=0.04). However, there were no significant differences in 1-year hospitalization rates for infectious, pulmonary, gastrointestinal or neurological complications between R-CHOP and CHOP groups, even in the aged  $\geq 80$  cohort.

**Conclusions:** This analysis confirms that the addition of rituximab to CHOP chemotherapy results in improved long-term overall survival even within an unselected population of patients with DLBCL and demonstrates for the first time that this benefit is also seen in very elderly patients.

### 338 TREATMENT OF PRIMARY MEDIASTINAL B-CELL LYMPHOMA – A MULTICENTER RETROSPECTIVE ANALYSIS ON BEHALF OF THE POLISH LYMPHOMA RESEARCH GROUP

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**Background:** The optimal therapy of primary mediastinal B-cell lymphoma (PMBL) remains a matter of debate. The aim of our study is to retrospectively compare four chemotherapy (CHT) protocols in respect of efficacy and toxicity.

**Methods:** Between 1999 and 2009 109 patients (pts) with PMBL (mean age: 31 yrs, female/male 1.45, LDH>N: 90%, PS>1: 45%, IPI>1: 50%) were treated with: R-CHOP-21 (19 pts), R-CHOP-14 (29 pts), R-CHOP followed by ESHAP and high-dose CHT with autoHCT (19 pts) and chemotherapy based on GMALL –B-ALL/NHL 2002 protocol (42 pts). (D Hoelzer et al. Blood 2007; 110: Abstr. 518). At the end of treatment, 88 pts (81%) received radiotherapy. Median follow-up: 35 months (range: 2–107).

**Results:** In all pts 5-year OS was 91% and PFS 78.5%. The treatment results after R-CHOP-21 were significantly worse compared to other protocols: 5-year OS for R-CHOP-21, R-CHOP-14, autoHCT and GMALL group were: 69%, 91%, 94% and 98% respectively (p=0.003). Similar findings were also observed in 5-year PFS - 20%, 77%, 89% and 93% (p<0.001). There was no significant difference in OS and PFS among R-CHOP-14, autoHCT and GMALL groups. There was a trend towards lower relapse rate after the most intensive GMALL regimen compared to R-CHOP-14 (7% vs 21%);

$p=0.09$ ). However, this regimen had the highest toxicity, mainly hematological, with one treatment-related death due to pulmonary aspergillosis. The Cox regression model confirmed the negative impact of R-CHOP-21 on PFS (HR=0.2;95%CI 0.07-0.49;  $p=0.001$ ).

**Conclusion:** In PMBL, R-CHOP-21 is associated with higher risk of treatment failure (death/disease progression/relapse) as compared to dose-dense and dose-intensified immunochemotherapy regimens.

### 339 CENTRAL NERVOUS SYSTEM INVOLVEMENT OF PATIENTS WITH BREAST LYMPHOMA

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**Background:** To retrospectively evaluate the incidence, treatment strategies, and outcome of breast non-Hodgkin lymphoma (NHL) patients (pts) with central nervous system (CNS) involvement.

**Methods:** We analyzed all patients with breast lymphoma documented at our center between 1976 and 2009. Treatment strategies and outcome were analyzed.

**Results:** Twenty-eight breast lymphoma patients were identified (female N=27, male N=1), median age was 59 yrs (range 25-73 yrs). Histologies were: DLCL (N=20), T-NHL (N=1), low-grade B-NHL (N=4), Burkitt lymphoma (N=1), other (N=2), 12/28 (43%) had CNS involvement. Of those, 2/28 initially presented with breast and CNS involvement; and 10/28 developed CNS involvement during progression with a median time of 56 months from diagnosis (range 15-281 mo). Initial treatment of all patients (N=28): Chemotherapy (CT)+radiotherapy (RT, N=14, of those N=3 additionally had breast surgery). CT alone (N=8), CT+ breast surgery (N=5), RT+ breast surgery (N=1), high-dose chemotherapy (HDCT) and stem-cell rescue (N=5), allogeneic stem cell transplantation (N=2). Over all, intrathecal (it) prophylaxis was applied in six patients. Rituximab was part of treatment in 11/27 B-cell lymphoma.

Treatment of pts with CNS involvement (N=12): CT alone (N=3), CT+RT (N=2), CT+ itCT (N=3), CT+itCT+RT (N=1), HDCT with stem-cell rescue (N=2), allogeneic stem-cell transplantation at CNS relapse (N=1). Three pts received Rituximab in combination with chemotherapy.

The 10-years over all survival (OS) rate of pts with breast lymphoma and systemic relapse was 83% and 56%, respectively. Pts with breast lymphoma and CNS involvement (relapse or initial manifestation) had a 10-yr OS of 18% with a median survival of 62 months.

**Conclusions:** We observed a high incidence of 12/28 (43%) of CNS involvement in our series of breast lymphoma patients. Treatment strategies varied strongly and prognosis of patients with CNS involvement is poor compared to those without.

### 340 POSTTRANSPLANT LYMPHOPROLIFERATIVE DISORDER (PTLD): CHARACTERISTICS AND OUTCOME IN A BELGIAN UNIVERSITY HOSPITAL

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**Introduction:** PTLD is a life-threatening complication of both solid organ and hematopoietic stem cell transplantation (Tx).

**Material and methods:** We undertook a retrospective analysis of all patients diagnosed with PTLD between January 1989 and December 2009 at the University Hospitals of Leuven, aiming to obtain information about incidence, pretreatment characteristics, treatment and outcome. Medical records of all patients were used for this retrospective observational study.

**Results:** 115 biopsy proven PTLD cases were included in this study. Overall incidence for all transplant types was 2%. Highest incidence was reported in heart-lung Tx (7.5%), followed by heart (4.9%), lung (2.9%), liver (2.7%), stem cell (1.4%), kidney (1.3%) and intestinal Tx (0%). Most PTLD were monomorphic (78.6%), with diffuse large B cell lymphoma (DLBCL) being the most frequent subtype, and presented with advanced stage (70%). The gastro-intestinal tract was the most frequently involved organ system (31%). Only 5% of the patients showed central nervous system involvement. The majority of cases (73%) occurred > 1 year post-Tx. 67.7% of the cases were EBV positive (early 90%, late 58.7%). At the moment of PTLD diagnosis immunosuppressive therapy included calcineurin inhibitors (92%), antimetabolites (71%) and low dose steroids (71%). Reduction of immunosuppression was performed in 90% of the cases. Other first line treatment modalities included rituximab (47%), chemotherapy (29%), surgery (11%) and radiotherapy (7%). Following first line therapy overall response rate was 69% (58% CR, 11% PR). At last follow up 41% of the patients were alive whereas 13% of the patients lost their graft during follow up. In univariate analysis overall response rate was associated with subtype ( $p=0.04$ ), normal LDH ( $p<0.0001$ ), lower ECOG performance state ( $p=0.01$ ) and lower Ann Arbor stage ( $p=0.02$ ).

**Conclusions:** We report a retrospective analysis of 115 cases of PTLD.

Overall incidence was almost 2%. As expected most cases were DLBCL, presented with advanced stage and had a poor outcome. 58.7% of late PTLD were EBV positive. Except for reduction of immunosuppression, treatment was very heterogeneous. Contrary to data from the literature the majority of cases occurred late following Tx, whereas rituximab therapy was not associated with a higher response rate in this analysis. Although the prognostic role of the international prognostic index (IPI) score in PTLD has been questioned, we were able to confirm its value in our analysis.

### 341 VEBEP REGIMEN AND HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) IN PATIENTS (PTS) WITH HD AND HIV INFECTION (HD-HIV): FINAL RESULTS OF A PHASE II STUDY OF THE ITALIAN COOPERATIVE GROUP ON AIDS AND TUMORS (GICAT) STUDY

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

**Methods:** CT included epirubicin 30 mg/m<sup>2</sup>/day (days 1-3), cyclophosphamide 1000 mg/m<sup>2</sup> (day 1), vinorelbine 25 mg/m<sup>2</sup> (day 1), bleomycin 10 mg/m<sup>2</sup> (day 3) and prednisone 100 mg/m<sup>2</sup>/day (days 1-3). HAART was given concomitantly to CT.

**Results:** From September 2001 to December 2008, 73 pts have been enrolled. The median age was 41 yrs. The median CD4+ cell count was 248/mm<sup>3</sup> and 51% of pts had a detectable HIV viral load. Stage III-IV was present in 50/71 (70%) pts. Histologic subtypes were: MC 70%, NS 20%, LD 4%, LP 2%, unknown 4%. Four toxic deaths (5%) were observed (septic shock, PCP, hepatic failure and pneumonia during neutropenia). An absolute neutrophil count <500 was noted in 60% of pts. Grade 3-4 anaemia was observed in 38% of pts and severe thrombocytopenia in 22% of pts. Twenty-two per cent of pts had febrile neutropenia with 19 documented infections in 16 pts (4 varicella, 4 bacterial pneumonia, 3 bacterial sepsis, 2 PCP, 1 cerebral toxoplasmosis, 1 oesophageal candidiasis, 1 HBV reactivation, 1 HCV reactivation, 1 prostatitis, 1 salmonellosis). CR was obtained in 49/73 pts (67%) and PR in 8/73 pts (11%). With a median follow up of 40 months (range 2-106), only 5 of CR pts have relapsed. The 3-yr OS and TTF at 24 months were 66% and 63%, respectively. An IPS greater than 2 (HR 2.87, 95%CI 1.08-7.63,  $p=0.03$ ) and a ECOG-PS greater than 1 (HR 2.79, 95%CI 1.21-6.44,  $p=0.02$ ) were significantly associated with a higher risk of death.

**Conclusions:** Our data demonstrate that VEBEP regimen in combination with HAART is feasible and active in pts with HD-HIV. As observed in HD of the general population, the IPS is able to stratify patients with different outcome.

This study was supported by ISS grants.

### 342 EFFICACY AND TOLERABILITY OF MODIFIED DOSE INTENSIVE R- CODOX-M/IVAC FOR HIV-ASSOCIATED BURKITT (BL) (AMC 048)

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**Background:** HIV associated BL remains controversial with concern for toxicity of dose-intensive regimens used in HIV negative patients (pts). Less intensive regimens have a high relapse rate. We modified CODOX-M/IVAC hoping to preserve efficacy while improving tolerability, particularly treatment related mortality (TRM).

**Primary object:** improving 1 year overall survival (OS) from the historical 65 to 85%.

**Methods:** Modifications of the US NCI regimen include rituximab (R), cyclophosphamide reduction [800 mg/m<sup>2</sup> x 2 days], vincristine 2 mg cap, methotrexate (mtx) 3000 mg/m<sup>2</sup>, dual chemotherapy lumbar punctures and IVAC infusion (high risk pts). Antibiotic prophylaxis & growth factor support specified, 100% grade IV hematopoietic toxicities in the original regimen. HAART therapy at the discretion of the local MD.

**Results:** Accrual of 33 planned pts by April 2010. Baseline: Classical Burkitt, 97%; Low/High Risk, 9/91%; Median (range) Age 42 (19 - 55); CD4 count 195 (0 - 721),

CD4 <100, 5 (27%); HIV viral load 1819 (Undetectable – 1,187,968). Median follow up (fu) is 9 mos for surviving pt.

Status	N (%)
Treatment Completed per protocol	21 (62%)
Disease Progression	3 (9%)
Early termination due to adverse event*	5 (15%)
Early termination due to patient withdrawal**	2 (6%)
Early termination – counts did not recover within time frame to begin cycle 4	1 (3%)
Treatment ongoing	2 (6%)

\*1 pt with grade (gr) 4 thrombocytopenia and gr 3 infection; 1 pt with gr 3 left hemiparesis; 1 pt with gr 3 confusion unrelated to treatment; 1 pt with prior hepatitis B and cirrhosis had gr 3 encephalopathy and pulmonary infiltrates; 1 pt with gr 4 neutropenia and gr4 thrombocytopenia. \*\*1 CR 2 yrs post treatment.

# of pts with gr3/4 toxicity: any 20 (61%), 13 (39%) hematologic, 16 (48%) infection including 7 febrile neutropenia, 6 metabolic with 1 tumor lysis syndrome, 4 neurologic, 2 thrombotic and 1 each coagulation, GI or pain. Only 2 gr 1/2 stomatitis/mucositis; 0 had gr 3/4.

Six deaths: encephalopathy with hepatic failure, hepatitis B and pneumonia (1), disease progression (3) including 1 in the CNS; fungal infection (1); HIV. Median 1 year OS (n=34) was 81.7% (61.0%, 92.1%) with a 35 mo median survival.

**Conclusions:** AMC 048 with a median fu of 9 mos has a 1 yr OS of 82% in BL. Relapses after 1 year are rare. TRM was zero. Notably, despite concerns raised in AMC 010 (DLBCL), R did not appear to increase toxicity. Only 5 pts withdrew due to AEs. Grade 3/4 toxicities were markedly reduced. Results compare favorably with 2 studies HIV neg pts. Magrath (1995) reported 100% grade 4 hematologic and 20% grade 4 mucositis in 39 adults, 33 children (92% 2 yr EFS). MRC/NCRI LY10 trial (Mead 2008) reduced mtx (3gr/m2), but reported 9% TRM (64% 2 yr OS).

### 343 IS LIPOSOME ENCAPSULATED DOXORUBICIN ABLE TO REDUCE THE CARDIOTOXICITY OF DOXORUBICIN IN THE TREATMENT OF DLBCL? A RANDOMISED STUDY BY THE AUSTRIAN WORKING GROUP OF MEDICAL ONCOLOGY (AGMT-STUDY NHL-14)

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**Introduction:** Rituximab, cyclophosphamide, vincristine, doxorubicin, and prednisone (R-CHOP) is the current standard treatment for diffuse large B-cell lymphoma (DLBCL). Doxorubicin is known to induce cardiac toxicity. By encapsulating doxorubicin in liposomes (L-DOXO) the cardiac toxicity may be reduced. This is the first randomised study comparing doxorubicin and L-DOXO in front line treatment of DLBCL.

**Patients and Methods:** Aim of the study was to reduce the cardiotoxicity of R-CHOP by replacing doxorubicin with liposome encapsulated doxorubicin. The primary endpoint was left ventricular ejection fraction (LVEF) measured with the Simpson method and NT-proBNP levels, respectively. From December 2007 to July 2010 we performed a two arm prospective randomised study. In arm 1 doxorubicin was replaced with L-DOXO 50 mg/m<sup>2</sup> iv day 1 of the standard R-CHOP regimen. In arm 2 standard R-CHOP was given. Six cycles were scheduled. Eighty-eight patients were registered, eight were excluded. In each arm 40 patients were eligible. Median age was 66 years (range 19-84 years), 64% of patients were older than 60 years. The two arms were balanced in respect to age, international prognostic index, NT-proBNP, and LVEF. At the time of the abstract submission 44 patients (24 and 20 in arm 1 and 2, respectively) had finished their treatment and were fully documented. The complete remission rate was 78.8% and 69.6% in arm 1 and 2, respectively. We observed 26 and 32 serious adverse events in 19 and 24 patients in arm 1 and 2, respectively. Most of them had neutropenic fever. Two of 24 (8.3%) and 5/20 (25%) had >20% decline of their LVEF during treatment in arm 1 and 2, respectively. However, this was not statistically significant. Median NT-proBNP levels were significantly higher (73.1 vs. 97.2 pg/ml) in arm 2 (P=.0235).

**Conclusion:** In this 1st analyses we did not observe any safety concerns in the two arms. Replacing doxorubicin with L-DOXO seemed not to alter the efficacy of the treatment. The difference in NT-proBNP levels may be an evidence for lesser cardiotoxicity of L-DOXO. The final analyses of the trial will be presented at the meeting.

### 344 CARDIAC MAGNETIC RESONANCE IMAGING FOR ASSESSMENT OF CARDIAC STRUCTURE AND FUNCTION FOLLOWING DOXORUBICIN-BASED CHEMOTHERAPY FOR NEWLY DIAGNOSED NON-HODGKIN LYMPHOMA

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**Background:** Doxorubicin is associated with an irreversible dilated cardiomyopathy, and its occurrence appears to be best predicted based on total cumulative dose of doxorubicin received. Recent studies suggest that previous reports may have underestimated the incidence of doxorubicin-induced heart failure (DIHF). To our knowledge, the time of onset of objective changes in both myocardial function and structure has yet to be well studied. Cardiac magnetic resonance imaging (cMRI) has the potential to identify the presence of fibrosis and early changes in systolic function. The objective of this study was to determine whether cMRI could be utilized to detect early structural and functional cardiac abnormalities in patients undergoing doxorubicin-based chemotherapy.

**Methods:** This was an initial proof of concept study in adults >19 years of age diagnosed with non-Hodgkin lymphoma who were planning to undergo doxorubicin-based chemotherapy. A baseline cMRI was performed prior to initiation of chemotherapy (MRI1) and a second cMRI (MRI2) was performed three months after completion of six cycles. An experienced investigator (TRP) interpreted each cMRI, and was blinded to all clinical data and whether studies were cMRI1 or cMRI2. Left and right ventricular ejection fractions were quantified for each cMRI. A reduction of >10% in ejection fraction between the two MRI studies was considered clinically significant. Delayed contrast images were analyzed to determine the presence of focal areas of fibrosis. Any finding of new delayed uptake was deemed as an event.

**Results:** Between 01/08 and 4/10, ten patients were enrolled on the trial. All 10 patients received a cumulative dose of doxorubicin of 300 mg/m<sup>2</sup>. Comparison of pre- and post-treatment cMRI demonstrated that five of 10 patients had a significant decrease in left ventricular ejection fraction (median -8.4%, range 1% to -17%). Three patients had at least one new segment of focal myocardial fibrosis.

**Conclusion:** We report an initial proof of concept study demonstrating that cMRI has the ability to assess both structural and functional myocardial changes in association with doxorubicin-based chemotherapy. We observed new and potentially important structural/functional cardiac changes in 70% of patients receiving a common cumulative dose of doxorubicin. The extent to which these changes predict for future clinically significant events is presently unknown. Further longitudinal analysis with a larger prospective cohort is planned.

### 345 CARDIOTOXICITY INCIDENCE AFTER CHOP-LIKE CHEMOTHERAPY WITH DOXORUBICIN/LIPOSOMAL DOXORUBICIN IN 571 LYMPHOMA PATIENTS

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**Introduction:** CHOP regimen and its modifications remain the mainstay of lymphoma treatment. Anthracycline related cardiotoxicity is a well described adverse effect. Liposomal doxorubicin (LipDox) was shown to be less cardiotoxic and recommended in frail patients.

**Materials and Methods:** Cardiotoxicity was assessed by medical history and LVEF measurement in 571 lymphoma patients: retrospectively in 540 cases treated with doxorubicin (Dox) and prospectively in 31 patients receiving liposomal doxorubicin (LipDox). All patients qualified for LipDox had a LVEF < 55% or NYHA I/II, hypertension, coronary artery disease and planned IFRT/ASCT consolidation. LipDox was also given, when LVEF dropped by > 15% or below 50% at the mid treatment assessment. Patient characteristics: average age 56 years (range 18-90), male to female ratio 301/269, clinical stage III/IV – 126/332, general symptoms – 384, large tumor burden – 48 cases, IPI 3-5 in 236 cases. There were 408 patients with DLBCL, 64 – MCL, 34 – FL, 35 – PTCL and 20 – MZL.

**Results:** At diagnosis average LVEF of Dox treated patients was 62.4% (40% - 85%), compared to 56.9% (40% to 77%) in LipDox cohort. The average cumulative dose was comparable in both groups (337 mg/m<sup>2</sup> and 301 mg/m<sup>2</sup> respectively). The difference between LVEF still visible at the mid treatment assessment (60.3 vs 56.4% respectively), disappeared at the end of therapy (54.8% vs 54.7%) due to less pronounced LipDox cardiotoxicity. Chemotherapy related cardiotoxicity was the second most common cause of death including 10/571 (1.8%) patients with acute cardiotoxicity and further 17/571 (3.1%) cases with early progressive chronic cardiotoxicity. None of them were so far reported in our LipDox treated patients.

**Conclusions:** LipDox administered to patients with high CVS risk at diagnosis, including low LVEF allowed for completing the scheduled chemotherapy without any excess cardiac toxicity.