indolent lymphoma

309 QUALITY OF LIFE MEASURES IN 'ASYMPTOMATIC' PATIENTS WITH FOLLICULAR LYMPHOMA (FL) AT PRESENTATION

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Background: In advanced 'asymptomatic' FL watchful waiting has been standard practice in many centres. However asymptomatic patients may have a reduced quality of life (QoL) that may be exacerbated by decisions not to treat the malignant disease. In the current UK NCRI Intergroup Trial asymptomatic patients are randomised between watchful waiting and Rituximab to investigate whether treatment with Rituximab results in a delay in the initiation of new therapy and an impact on QoL. The results of the baseline QoL and the impact of randomisation are reported here.

Methods: QoL was assessed before randomisation and 1 week after. The instruments used for this analysis were Functional Assessment of Cancer Therapy-General (FACT-G) and Hospital Anxiety and Depression instrument (HAD). FACT-G scores were standardised on a 100-point scale and summarised by means. A score of 100 indicates perfect health status. HAD subscales were grouped as normal, borderline and case.

Results: 252 patients participated in the QoL study with a compliance rate of >80%. Median age was 59 years and 45% were male. The mean FACT emotional wellbeing was reduced compared to the normal population. There was an increase of patients deemed to have anxiety on the HAD score (case 11.2% vs 2.6%) but the total number of cases and borderline patients was unchanged. There was no overall change in QoL measures after randomisation.

Conclusions: Only a few patients with asymptomatic advanced FL in this trial had significant anxiety or depression and the process of randomisation was not deleterious.

310 AN INDOLENT COURSE AND T(14;18) IN PRIMARY DUODENAL FOLLICULAR LYMPHOMA

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Background: Little is known about the primary duodenal follicular lymphoma (DFL).

Patients and Methods: Twenty-seven patients with primary DFL diagnosed at the National Cancer Center Hospital between 1999 and 2007 were subject to clinico-pathological analysis. Cytogenetics using FISH to detect IGH/BCL2 fusion were carried out.

Results: Nineteen patients (70%) had no symptoms at the time of diagnosis. The most common site of involvement was the descending part of the duodenum (89%). According to the staging system of gastrointestinal tract lymphoma by Rohatiner *et al.*, 17 patients had Stage I, 7 had II and 3 had IV. FL International Prognostic Index (FLIPI) risk was low in 25 patients (92%) and intermediate in 2 (8%). Nineteen patients (70%) had histological grade 1, 7 (26%) had grade 2 and 1 (4%) had grade 3a. IGH/BCL2 fusion was present in 20 (83%) among 24 patients examined. This figure was high compared with that obtained in a previous study of Japanese patients with nodal FL, where 60% of the patients demonstrated the fusion. All the patients have survived with a median follow-up time of 30.9 months (3.4-100.4). One patient was lost for follow-up. Eleven patients received no treatment initially; their estimated therapy-free survival rates after 1, 2 and 3 years were 80%, 60% and 60%, respectively, with a median follow-up time of 11.1 months (3.4-69.5). Fifteen patients received therapy upon diagnosis (local radiotherapy in 3 patients and chemotherapy in 12 including rituximab therapy); their overall response rate was 80%, and their estimated progression-free survival rates after 1, 2 and 3 years were 85%, 57% and 57%, respectively, with a median follow-up time of 17.9 months (3.2-78.1). Among the 3 patients who received local radiotherapy, only one (4%) developed histological transformation with relapse at the cervical lymph node.

Conclusions: The majority of primary DFL is positive for t(14;18), localized, of low grade morphology and with low FLIPI risk. A watch and wait policy might be an alternative approach for its indolent course; however, further studies are warranted.

311 FOLLICULAR LYMPHOMA IN YOUNG PATIENTS (<50 YRS): A POPULATION-BASED ANALYSIS OF THE DANISH LYMPHOMA REGISTRY

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Background: Follicular lymphoma (FL) is an incurable disease with a median survival of 7-10 yrs and a median age of 60-65 yrs at diagnosis. However, FL also occurs in younger pts where intensified therapies may be curative. Data on younger FL pts (yFL) are scarce. The purpose of this analysis was to provide specific data for yFL (age 15-49 yrs) via the Danish population-based LYFO registry.

Patients and Methods: Histological diagnoses were validated by a pathology panel. All reported clinico-pathological features are pre-therapeutic. Incidence rates were standardized according to the European standard population (sIR).

Results: In total, 1551 FL cases (median age: 59 yrs) were diagnosed in the period 1983-2004. Of these, 26% (n=399) were yFL (median age: 43 yrs, range 15-49 yrs). Their median follow-up was 10 yrs (range: 4 days–22 yrs). In contrast to the total FL population, showing a moderate incidence increase throughout the study period, yFL had a stable sIR rate of ca $1.0/10^5$/yr. Histologically, 9% of yFL had grade 3 morphology, 71% had disseminated disease and 7% primary extranodal lesions. In 14% of yFL, s-LDH was elevated at presentation. Of 112 cases undegoing biopsy at relapse, 20% revealed histologic transformation. The corresponding value in the FL cohort ≥50 yrs was 30%. The overall survival curve for yFL showed a linear decrease with a median survival of 15.5 yrs as compared to 7.2 yrs for the older cohort.

Conclusion: The present data on incidence, clinico-pathological features and survival in yFL provide a baseline comparative tool for the elaboration of yFL-specific prognostic models and clinical trials.

312 PATTERNS AMONG FOLLICULAR LYMPHOMA PATIENTS IN SEER-MEDICARE

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Background: Recent data from randomized clinical trials and observational studies demonstrate improved progression free and overall survival among follicular lymphoma (FL) patients. The objective of our study was to evaluate the effect of patient characteristics, disease severity and chemoimmunotherapy regimens (CT) on survival.

Methods: Using the SEER-Medicare dataset, we identified patients with a first primary FL diagnosis (by histology) between 1998-2002, with follow up through 2005.We evaluated survival times in months from diagnosis date to date of death. Time to death was assessed using Cox proportional hazards regression with censoring for end of coverage. Models were adjusted for age, gender, histology, stage, and anemia or lymphocytopenia diagnosis within 1 month of the FL diagnosis. We identified claims for CT and rituximab (R) in the first three months following diagnosis.

Results: 2,053 patients met the inclusion criteria. The mean age was 75.7.The median survival time (censoring for end of coverage) was 56 months (95% CI 24 – 84 months). *First CT* regimens were distributed as: CT with R (30.4%), CT without R (29.5%) and No treatment in three months following diagnosis (40.0%). Increasing age and stage, and the presence of anemia or lymphocytopenia were significantly associated with shorter times to death ($p<0.05$). Female gender, Grades 1/2 follicular histology (vs. histology not otherwise specified), and CT with R (vs. CT without R) were significantly associated with longer times to death ($p<0.05$).

Conclusions: CT with R vs. CT without R is associated with increased survival time in the Medicare population diagnosed with FL between 1998 and 2002. Additionally, female gender, Grades 1/2 follicular histology were significantly associated with greater survival ($p<0.05$).

Survival of follicular lymphoma Medicare patients

	HR	HR 95% CI
Female	0.797	0.701–0.906
Age		
65–75	ref	
75–5	1.764	1.527–2.038
85–95	3.794	3.131–4.597
>95	8.573	4.197–17.513
Histology		
Unspecified (9690)	ref	
Grade 1 (9695)	0.759	0.639–0.901
Grade 2 (9691)	0.766	0.643–0.913
Grade 3 (9698)	0.932	0.771–1.128
Stage		
1	ref	
2	1.343	1.084–1.663
3	1.772	1.466–2.140
4	2.159	1.814–2.571
None	1.206	0.924–1.574
Chemo in the first 3 months		
CT without R	ref	
CT with R	0.602	0.501–0.722
NoTx	1.147	0.983–1.339
Anemia diagnosis	1.583	1.373–1.825
Lymphocytopenia diagnosis	1.507	1.088–2.088

313 GRUPPO ITALIANO STUDIO LINFOMI (GISL) CRITERIA FOR DEFINING DISEASE-PROGRESSION IN INDOLENT NON FOLLICULAR LYMPHOMA

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The GISL prospectively evaluated 157 pts with INFL meeting criteria of no therapy for at least 3 months after diagnosis included in different GISL centers between July 1993 and December 2004. Pts were considered eligible for this prospective study if they had a diagnosis of SL, LP, SMZ or NMZ, extranodal non-gastric MALT. Indolent disease was defined by the absence of followings: B symptoms, bulky disease (i.e. a nodal involvement > 5 cm), Hb level < 10 g/dL, PLT count < 100 x 10^9 /L, diffuse pattern of BM involvement and a quick increase in the size of nodal involved sites (i.e., doubling time < 12 mo.). After a median follow-up time of 48 mo. (range, 3-169) 37 out of 139 evaluable pts experienced significant disease-progression and consequently indication for treatment. The proportion of pts not requiring chemotherapy at 3, 5 and 8 yrs was 80% (95% CI: 72-86%), 72% (95% CI: 62-80%) and 63% (95% CI: 51-74%), respectively. Factors associated with a shorter time to first treatment (TFT) were hystotype (LL/LP vs SMZ/NMZ or non-gastric MALT; Hazard ratio [HR], 2.51; P=0.01), number of nodal sites involved (<4 vs >4; HR, 3.07; 0.02), ESR (HR, 1.01; P=0.04) and FLIPI (HR, 2.02; P< 0.05). Pretreatment parameters that remained independently associated with shorter TFT in multivariate analysis were SL/LP histology (HR 3.08, 95% CI, 1.45-6.54; P=0.004) and FLIPI 3-5 (HR 3.05, 95% CI, 1.42-6.55; P=0.004). Interestingly, histology corrected by FLIPI led to a 37% increase of regression coefficient, thus FLIPI increases the discriminant power of histology. As a matter of fact, median TFT was significantly longer in pts with SL/LP histology and FLIPI 0-2 in comparison to pts with same histology and FLIPI 3-5 (median TFT 106 vs 15 mo.). The same did not apply for pts with SMZ/NMZ or non-gastric MALT histology (P=0.518). We confirm that SMZ/NMZ or non-gastric MALT lymphoma have a different clinical behaviour in comparison to SL or LP lymphoma and should be considered as different entities. FLIPI represents an important step in identifying patient subgroups with predictable outcome among those with SL/LP lymphoma.

314 SOLUBLE CD27 LEVELS ARE CORRELATED WITH DISEASE STAGE AND RESPONSE TO TREATMENT IN WALDENSTRÖM'S MACROGLOBULINEMIA (WM)

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Introduction: Soluble CD27 (sCD27), a TNF-R family member which supports the survival of WM tumor cells through CD40L signaling, is elevated in the sera of patients with WM and appears to be a reliable marker of disease burden (Ho et al, Blood, 2008). We therefore sought to determine its potential role in the prognosis and staging of WM patients.

Methods: We retrospectively assessed the baseline levels of sCD27 in 149 previously-untreated WM patients by ELISA (Bender Mendsystems). Sera from healthy, age-matched donors (HD) was used as a control. sCD27 levels were examined in association with the ISS prognostic system that has been reported to affect clinical outcome in WM (Dimopoulos et al, 2004). The statistical analysis was performed using the SAS software.

Results: sCD27 levels were significantly higher in WM patients (median 90.08, range 42.81- 525.61) compared to HD (median 45.7, range 24.7-87.7 U/mL) (p<0.0009), with 109/149 (73%) patients demonstrating sCD27 levels which were higher than the mean level observed in healthy donors. Importantly, we observed a correlation with higher sCD27 levels and more advanced ISS staging. Mean sCD27 levels among the 3 ISS groups using ANCOVA analysis were as follows: stage I (n=93) 99.88 vs. stage II (n=34) 136.74 vs. stage III (n=10) 168.75 U/mL (p=0.0274). No significant differences in sCD27 levels between symptomatic and asymptomatic patients wereobserved. Lastly, among patients in this cohort who subsequently received treatment, we observed higher rates of response (34/50 (68%) vs. 16/50 (32%); p=0.0006) among patients with sCD27 levels >47 U/mL.

Conclusions: sCD27 levels are elevated in patients with WM, and correlate with the WM ISS staging system. Moreover, sCD27 may predict response to therapy in patients with WM.

315 SERUM IMMUNOGLOBULIN AND FREE LIGHT CHAIN ABNORMALITIES IN NON HODGKIN LYMPHOMA

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The presence of an abnormal serum free light chain (FLC) ratio is a poor prognostic indication in all monoclonal plasma cell diseases. The availability of antibodies specific for immunoglobulin heavy chain/light chain pairs (eg IgAκ or IgAλ) has made it possible to measure similar ratios for immunoglobulins. Here we report baseline observations in a study of FLC and intact immunoglobulin ratios in patients with non Hodgkin lymphoma (NHL). Presentation sera from 93 patients (8 Waldenstrom's macroglobulinaemia-WM and 85 NHL) were analysed. Results were compared with the published normal range for FLC or data from 100 blood donor sera for the intact immunoglobulin ratios. Quantitative abnormalities were identified in the sera of 57% (53/93) of the patients with 48% (45/93) by the novel immunoglobulin assays, compared with 18% (17/93) using standard serum protein electrophoresis. The frequency of abnormalities varied markedly between diseases eg. 100% (8/8 WM), 65% (13/20 diffuse B cell lymphoma), 63% (17/27 marginal zone lymphoma) or 29% (5/17 follicular lymphoma). The most frequent abnormalities were in the serum FLC ratio (22/93) and IgDκ/IgDλ ratio (18/93). For both these ratios the abnormalities predominantly indicated an excess production of the κ form (20/22 for FLC and 18/19 for IgD) but in only one patient were the FLC and IgD simultaneously abnormal. FLC abnormalities were found mostly (14/22 patients) in combination with an abnormal ratio in one of the intact immunoglobulins. Intact immunoglobulin abnormalities were usually present (37/46 patients) in only one immunoglobulin class, as would be expected in monoclonal disease. Abnormally low concentrations of IgM (with normal IgMκ/IgMλ ratios) were found in 28% (26/93) of the sera but this degree of immunoparesis was not seen with the other immunoglobulins or FLC. The study needs to be extended to determine whether the FLC and immunoglobulin ratios have utility for prognosis or disease monitoring in NHL.

316 TREATMENT OUTCOME AND LIVER TOXICITY IN OF HCV-POSITIVE NON-HODGKIN'S LYMPHOMA: A STUDY ON 160 PATIENTS

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We studied 160 HCV+ pts with NHL treated from 1995 to 2007 at our institution: 59 indolent NHL, 101 aggressive NHL, median age 67 yrs (range 32-88), M/F 69/91, AA stage I-II in 32%, III-IV in 68%. IPI was low in 28%, int/low in 28%, int/high in 28%, high in 16%. At least one extranodal localization was present in 76%, 33% had splenic involvement. HCV-RNA was present in 146/149 tested. 15% of pts had cryoglobulins. HBsAg was positive in 7 pts. At diagnosis ALT value was above UNL in 67 pts (in 31 > 2 x UNL, in 13 > 3 x UNL). 126 ptsreceived an anthracycline-based therapy, 34 alkylators, 28 received chemotherapy plus Rituximab. Cytotoxic drugs dose was reduced in 63 pts (median reduction of 33%, range 20-50%). Steroids were reduced or stopped in 27 pts (18 for liver toxicity). Among 93 ptswith normal ALT at presentation, 10 developed WHO grade II liver toxicity and 6 grade III. Among 67 ptswith abnormal ALT 8 had a 3.5 times elevation during treatment. Overall 24 pts(15%) developed significant liver toxicity. Among 28 ptstreated with Rituximab, and chemotherapy, 5 (18%) developed liver toxicity; among other132 ptswho received

chemotherapy only 9 (7%) had hepatotoxicity (p=0.08). 57% achieved CR and 22% PR; 34 pts (21%) did not complete planned treatment (20 progression, 8 liver toxicity, 6 non-liver toxicity). Median PFS for pts who experienced liver toxicity is significantly shorter than median PFS of pts without liver toxicity (respectively 2 yrs and 3.7 yrs, p=0.03). After a median F-UP of 2 yrs, 32 pts died (22 NHL, 3 hepatic failure, 7 other causes). In conclusion, a significant proportion of pts with HCV+ NHL develop liver toxicity often leading to interruption of treatment. This is an important limit to the application of effective modern immuno-chemotherapy programs. HCV+ lymphomas represent a distinct clinical subset of NHL that deserves specific clinical approach to limit liver toxicity and ameliorate survival.

317 PROGNOSTIC INFLUENCE OF TUMOR-INFILTRATING MAST CELLS IN FOLLICULAR LYMPHOMA PATIENTS TREATED WITH RITUXIMAB AND CHOP

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Introduction: Gene expression profiling and immunohistochemical studies have demonstrated that nonmalignant tumor infiltrating inflammatory cells contribute to clinical outcome of FL patients. Particularly, tumor-associated macrophage (TAM) content correlates with longer survival rates in immunochemotherapy-treated patients. The purpose of this study was to investigate the prognostic importance of tumor-associated mast cells (MCs) and their relation to TAMs in FL patients treated with combination of rituximab® and CHOP chemotherapy.

Materials and Methods: Tumor samples from 98 FL patients, of whom 70 received R-CHOP at diagnosis and 28 at relapse, were stained with Leder stain for naphthol-ASD-chloroacetate esterase, or antibody against tryptase to detect MCs. MC content was correlated with survival parameters.

Results: A significant correlation was observed between Leder stain and tryptase positive cell counts (r_s=0.658; P<0.001). According to Kaplan Meier estimates, the patients with high MC content had a worse 5-year progression free survival (PFS) after R-CHOP therapy (33% vs 66%, p=0.0020). The adverse prognostic value of MCs was seen both for the patients treated at diagnosis and at relapse, whereas no such impact on PFS was observed for the control patients treated with chemotherapy only (p=0.4). When the TAM-related PFS was analyzed separately in patients with high and low MC contents, the positive prognostic effect of TAM was seen only in patients with few MCs.

Conclusions: The data demonstrate that high MC score is associated with unfavourable prognosis and it eliminates the positive prognostic value of TAMs in FL patients treated with immunochemotherapy.

318 MDM2 309 AND TP53 ARG72PRO SNP GENOTYPES DO NOT PREDICT CLINICAL OUTCOME OF FOLLICULAR LYMPHOMA

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Introduction: Sequential biopsy analysis has shown the relevance of *TP53* mutations and MDM2expression in progression of Follicular Lymphoma (FL). Tumour associated Single Nucleotide Polymorphisms (SNPs) alter the function/expression of these genes. The *MDM2* 309 T>G SNP is associated with increased expression of MDM2 and earlier onset, increased risk or worse prognosis of several solid tumours and the *TP53* Arg72Pro G>C SNP is associated with increased risk of some tumours. We sought to establish if *MDM2* SNP 309 either alone or in combination with the *TP53* Arg72Pro SNP predicts outcome and transformation of FL.

Material and Methods: DNA from bone marrow / peripheral blood / lymph nodes of 240 patients with FL (including 81 transformed cases) were obtained from the tissue archive at St. Bartholomew's Hospital. Average age at diagnosis was 49 years. Samples were analysed for *MDM2* 309 and *TP53* Arg72Pro SNPs via an Allelic Discrimination multiplexed endpoint assay (Applied Biosystems). Direct sequencing on a subset of samples confirmed the results. Samples were selected on DNA availability.

Results: Allele frequencies of the cohort were similar to previously published results (for *MDM2* SNP 309 these were TT 44%, TG 44%, GG 12%; for *TP53* Arg72Pro these were GG 47%, GC 46%, CC 7%). Average ages at diagnosis for the genotypes were similar to that of the cohort being 48, 48 and 49 years respectively for *MDM2* SNP 309 and 49, 49 and 47 years respectively for *TP53* Arg72Pro. There was no association of *MDM2* SNP 309 genotypes (either in isolation or in combination with *TP53* Arg72Pro SNP genotypes) with gender, stage at diagnosis, response to first line therapy or best response to therapy nor overall survival, progression and relapse free survival or time to transformation.

Conclusion: Although deregulation of the MDM2-TP53 pathway is a feature of FL and its progression, reported variants (*MDM2* 309 and *TP53* Arg72Pro) do not predict its clinical course.

319 EXPRESSION OF THE P16^{INK4A} TUMOR SUPPRESSOR CORRELATES WITH ADVERSE CLINICAL OUTCOME IN FOLLICULAR LYMPHOMA

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Background: Follicular lymphoma (FL) is an attractive model for discovering biomarkers and elucidating mechanisms of tumor progression. We hypothesized that alterations in the expression of proteins with known roles in hematological cancers might correlate with clinical outcome and thereby shed light on biological mechanisms.

Methods: Sections from a tissue microarray (TMA) containing FL samples from 67 patients were immunostained for candidate biomarkers, including p53, p16^{INK4a}, bcl-2, bcl-6, MUM1, p65, PML, pERK, and p27. The Kaplan-Meier method and log-rank test were used to identify markers that correlate significantly (p<0.05) with overall survival (OS). Multivariate analysis of significant variables was undertaken using a stepwise Cox proportional hazard method. The chi-squared or Fisher exact test were used to examine associations between histological markers and baseline clinical features, including the FLIPI score.

Results: Expression of p16^{INK4a} or p53, or absent CD10 expression correlated with poor survival. Patients with p16-negative tumors had a median OS of 13.4 years (95% CI: 1-26) compared to 8.3 years (95% CI: 0-17) for those with p16-positive tumors (p=0.006). Expression of p16^{INK4a} was significantly associated with low hemoglobin, elevated serum LDH, high histological grade, high cell proliferation index, presence of associated diffuse large B-cell lymphoma (DLBCL) and high-risk FLIPI classification. Multivariate analysis identified lack of CD10 and p16-positive expression as significant and independent predictors of OS.

Conclusion: Our observation of a positive association between p16^{INK4} expression and indicators of tumor aggressiveness is novel and perhaps surprising since loss of the *INK4a* tumor suppressor gene is one of the most frequently observed lesions in human cancers, including lymphoma. Expression of p16^{INK4a} may reflect induction consequent to unidentified pro-mitotic mutations associated with more aggressive instances of FL.

320 STRUCTURAL REARRANGEMENT DISCOVERY IN FOLLICULAR LYMPHOMA GENOMES

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Introduction: We are using microarray and Bacterial Artificial Chromosome (BAC) based technologies to identify, clone and characterize genome rearrangements in 24 follicular lymphoma (FL) genomes. Our approach is designed to identify large-scale and small-scale differences between tumor genomes and the reference human genome sequence.

Methods: BAC libraries constructed from each of 24 FL tumor samples are subjected to restriction fragment fingerprinting. Genome maps are constructed and each fingerprint is independently aligned to the reference human sequence to determine the genomic region represented and identify candidate tumor genome rearrangements. The results are integrated with BAC aCGH and Affymetrix 500K SNP array assays, which identify gains and losses of genomic intervals (CNVs).

Results: BAC library construction and fingerprinting is complete for 15 tumor samples. Fingerprint analysis identifies translocations, inversions, deletions and insertions on the order of 100kb to several Mbp in size including the expected t(14;18). Thousands of small-scale candidate rearrangement events have also been identified; many of these correspond to small deletions or SNPs. Sequence analysis of small and large scale rearrangements is underway. BAC aCGH and Affymetrix SNP arrays identify 1-14 CNVs in each of 22 patients. The CNVs identified using microarrays tend to be much larger than events identified with BAC fingerprints. Copy number neutral LOH events are also observed.

Conclusions: Our multi-method approach is effective for high-resolution, large-scale cloning and analysis of entire FL genomes, and reveals an unanticipated number of small (kilobase-scale or smaller) candidate rearrangements. Early results suggest that many of these are found in both normal and tumor DNA samples, suggesting the

possibility that some of the rearrangements may represent alleles that pre-dispose to disease.

321 EXAMINATION OF CHANGES IN TUMOUR MICROENVIRONMENT OF FOLLICULAR LYMPHOMA USING SERIAL SAMPLE TISSUE MICROARRAYS

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Background: There is mounting evidence that the immune microenvironment in FL is important in patient outcome, but little data on the changes in immune microenvironment over disease progression and impact on outcome. The goal of this study was to examine the immune microenvironment in patients with FL over the course of their disease and correlate this to transformation and overall survival (OS).

Materials and methods: TMAs were constructed of 1mm cores in triplicate from 45 patients with more than 2 biopsies during the course of their FL. The number of biopsies ranged from 2 to 6 and initial diagnostic biopsies were always included. Immunohistochemistry was performed on the TMAs using a panel of antibodies detecting antigens on T cells, regulatory T cells (FOXP3), macrophages (CD68) and follicular dendritic cells (FDC). The immune infiltrates were scored for number and location. The FDCs were scored on the presence of the FDC meshwork (disrupted versus non disrupted).

Results: The median age of the patients at diagnosis was 48.5 years (range 26-77), median FLIPI score was 3 (n=36), median stage was 4 (n=36). Fifteen of the patients transformed to DLBCL. Median OS was 96 months and the median time to transformation was 76 months. Changes in the levels of immune infiltrating cells in serial biopsies were analysed. Patients in whom the number of CD68+ cells decreased or remained <5 cells/hpf (n=21) had an increased median time to transformation (49 months) and overall survival (100.5 months) as compared to patients in whom the number of CD68+ cells increased or remained >5 cells/hpf (n=19). The time to transformation in these patients was 25 months and OS was 71 months. Alterations in the numbers of T cell subsets and integrity of the FDC meshwork were not associated with time to transformation or OS.

Conclusions: The results reaffirm the complex nature of the interaction between the immune microenvironment and the FL cells. Patients with biopsies containing persistently high numbers of CD68+ cells at any point in their disease have a worse outcome than patients with low numbers.

322 GENETIC ALTERATIONS ASSOCIATED WITH RELAPSE AND PROGRESSION OF FOLLICULAR LYMPHOMA STUDIED IN SERIAL BIOPSIES

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Follicular lymphoma (FL) in advanced stages is an incurable disease with variable clinical course. A significant proportion of the patients transform to a more aggressive lymphoma, usually diffuse large B cell lymphoma with dismal prognosis. The remaining patients experience progressive and relapsing FL without transformation until the disease becomes resistant to treatment. Several genetic abnormalities have been associated with the histological transformation of FL. Furthermore, several studies have investigated the prognostic significance of genetic alterations and clinical parameters at the time of diagnosis. In contrast, the genetic alterations associated with progression and relapse of FL without histological transformation have been less studied. We have access to a unique material consisting of serial biopsies (2 to 4) from 35 patients with progressive and relapsing FL with clinical data available. The aims of this study were to i) identify DNA copy number alterations (CNA) associated with progression and relapse of follicular lymphoma, and ii) identify CNA associated with an indolent or aggressive disease course, and iii) correlate CNA with gene expression data to identify target genes in relapsing follicular lymphoma. Array based comparative genomic hybridization (aCGH) was performed to examine CNA in the serial biopsies using in-house CGH arrays containing approximately 4.500 BAC/PACs in quadruplicate with the resolution of 1Mb. Software for aCGH data analysis were Normalization Suite and CGHsmooth. The Human Genome U133 Plus 2.0 gene chip from Affymetrix was applied to investigate gene expression in the same biopsies. Preliminary data suggest that acquisition of genetic changes is not a linear process and support the existence of tumor ancestor cells in FL. We are currently correlating the aCGH data to clinical parameters and to the corresponding gene expression data.

323 PROGNOSTIC FACTORS INFLUENCING THE OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS IN THE GELA-GOELAMS FL2000 STUDY

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Results of the randomized FL2000 study comparing chemotherapy plus aIFN (CHVP+I) versus Rituximab plus CHVP-I in 358 follicular lymphoma patients (pts) were recently updated and demonstrated a superior outcome for patients receiving R-CHVP-I: 5-year event-free survival (EFS) estimates were respectively of 37% and 53% in the CHVP+I and R-CHVP+I arm (P=.0004) (Salles et al. ASH2007). However, an overall survival (OS) advantage appeared to be restricted to pts presenting a high (≥3) FLIPI score (P=.025). Outcome was markedly different in each FLIPI subgroup. To further characterize which pts benefited of the addition of rituximab, we examined individually each of the FLIPI factors. Age over 60 years, Ann Arbor stage III-IV (AA stage), haemoglobin level < 12 g/dL (Hb), LDH level above normal value (LDH), and number of nodal sites > 4 (nodal sites) were then tested for their influence on patient's outcome in the whole trial and in the 2 separate study arms. Considering all patients in univariate and multivariate analyses, age did not significantly influenced EFS, while AA stage, nodal sites, LDH, and Hb all did. However OS was significantly affected by age, LDH and Hb but not by nodal sites or AA stage. Other factors such as B symptoms, number of extranodal sites, bone marrow involvement, B2-microglobulin and albumin levels did not significantly affected the multivariate models. Considering CHVP-I pts, multivariate analysis identified nodal sites (RR=1.64; P=.0002), LDH (RR=1.84; P=.0016) and Hb (RR=2.15; P=.043) as predictors of EFS as well as age (RR=2.83; P=.0053), LDH (RR=2.30; P=.014) and Hb (RR=2.59; P=.019) as predictors of OS. In contrast in R-CHVP-I pts, only nodal sites (RR=1.89; P=.0117) predicted EFS and Hb (RR=2.55; P=.02) and LDH (RR=2.29; P=.042) OS. We conclude that 1) among FLIPI factors, the number of nodal site appears to be a strong predictor of EFS in pts receiving or not rituximab while age, LDH and Hb levels are strong predictors of OS and 2) that OS of in rituximab treated pts is influenced by Hb and LDH levels but not by age or others factors.

324 PCR FOR BCL-2/IGH+ CELLS IN STAGE I/II FOLLICULAR LYMPHOMA IDENTIFIES POSITIVE CELLS IN BONE MARROW AND PERIPHERAL BLOOD OF THE MAJORITY OF PATIENTS, THAT CAN BE CLEARED BY LYMPH NODE IRRADIATION

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Background: Stage I/IIA follicular lymphoma (FL) is considered a localized disease that can be adequately treated with radiotherapy alone. Minimal Bcl-2/IgH+ cell contamination in the peripheral blood (PB) or bone marrow (BM) can be detected by qualitative and quantitative PCR. Aim of this study was to evaluate the role of PCR, the impact of radiotherapy and prognosis in localized FL.

Methods: PB and BM Bcl-2/IgH+ cell involvement in FL was investigated by PCR in a series of 25 consecutive stahe I/IIA patients with histologically-revised diagnosis and treated with involved field radiotherapy alone.

Results: Despite a negative BM biopsy, Bcl-2/IgH+ cells were found at diagnosis in the PB and/or BM of 17 patients (68%). After lymph node involved field radiotherapy, in 10/16 Bcl-2/IgH positive evaluable patients, a disappearance of Bcl-2/IgH+ cells was observed, which persisted after a median follow-up of 42 months (range 5–79) in all but 2patients. Quantitative PCR demonstrated the feasibility of clearing PB and BM Bcl-2+ cells after local irradiation of the primary site of the disease only when the basal number of lymphoma cells was <1:100,000. One patient had a molecular relapse only and was reinduced into a negative PCR status after rituximab treatment. Clinical relapse was observed in 4/25 patients; all of them had Bcl-2/IgH+ cells in the PB and/or BM at diagnosis. After radiotherapy, 3 of them persisted Bcl-2 positive in BM and/or PB and 1 became negative.

Conclusions: In the majority of localized FL, Bcl-2/IgH+ cells could be found in the PB and BM despite a negative BM biopsy. Lymphoma cells can thus reversibly spread from the affected lymph node(s) to PB and BM, and durably disappear after lymph nodeirradiation. Patients with Bcl-2/IgH+ cells at diagnosis or after treatment had a higher likelihood of relapse. The possibility of a persistent lymphoma cell clearance is proportional to the amount of cells detected at presentation by quantitative PCR. Rituximab can reverse molecular relapses.

325 IMMUNO-PET/CT IMAGING WITH ^{89}ZR-RITUXIMAB AS A PRELUDE FOR RADIOIMMUNOTHERAPY WITH ^{90}Y-RITUXIMAB IN PATIENTS WITH RELAPSED CD20+ B-CELL NON-HODGKIN'S LYMPHOMA

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Background: Immuno-PET combines the high sensitivity of PET with the specificity of a monoclonal antibody (mAb). Zirconium-89 is a positron emitter with a half-life of 78.4 hours, which is compatible with the time needed for an intact mAb to achieve optimal tumour-to-background ratios. The antigen CD20 provides an excellent target because it is expressed on the surface of most B cells and is neither shed nor internalized on antigen binding. The aim of this study was to evaluate the performance of ^{89}Zr-rituximab immuno-PET/CT in patients with CD20+ B-cell NHL.

Materials and Methods: Five patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma were included in this study. Similarly to the Zevalin® treatment schedule, each patient received a first infusion of (cold) rituximab at 250 mg/m^2 followed by the injection of 3-4 mCi ^{89}Zr-rituximab and one week later, the same infusion of rituximab followed by radioimmunotherapy with ^{90}Y-rituximab. ^{89}Zr-rituximab-PET/CT was performed at 4 time points: 1 hour, 24 hours, 3 days and 6 days after the intravenous injection of ^{89}Zr-rituximab. A baseline ^{18}FDG-PET/CT was performed 1 to 4 weeks before the start of the study and was compared with the findings of the ^{89}Zr-rituximab immuno-PET/CT. For the evaluation of pharmacokinetics, blood samples were taken at the following time points: 5, 15 and 30 min, and 1, 2, 4, 16, 24h and 3 and 6 days after completion of infusion of ^{89}Zr- and ^{90}Y-rituximab.

Results: PET/CT imaging with ^{89}Zr-rituximab provides high quality images up to 1 week after the injection of 3 mCi of ^{89}Zr-rituximab. The highest lesion to background ratio was found on the late images (6 days p.i.). Two out of 5 patients showed more lesions on ^{89}Zr-rituximab PET/CT compared to ^{18}FDG-PET/CT.

Conclusion: These preliminary findings show that ^{89}Zr-rituximab immuno-PET/CT imaging provides high quality images up to 1 week after the injection of the tracer and is an excellent imaging tool for dosimetry as a prelude for radioimmunotherapy with ^{90}Y-Rituximab.

326 PROGNOSTIC SIGNIFICANCE OF MOLECULAR REMISSION IN FOLLICULAR LYMPHOMA AND IMPACT OF CONSOLIDATION TREATMENT

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Introduction: Detection of minimal residual disease (MRD) by RQ PCR is an important tool for therapy monitoring in follicular lymphoma (FL) and may predict the clinical course also after autologous stem cell transplantation (ASCT). We evaluated the prognostic value of MRD assessment within the prospectively randomized multicenter trial of the German low-grade lymphoma study group (GLSG) for patients with advanced FL receiving R-CHOP/CHOP induction followed by ASCT or interferone maintenance.

Patients and methods: MRD was analysed by t(14;18) RQ PCR in blood (PB) and bone marrow (BM) of 80 patients with advanced stage, t(14;18) positive FL prospectively randomized within the trial and treated frontline with CHOP (n=42) or R-CHOP (n=38).

Results: MRD quantification in PB after CHOP induction demonstrated a significant reduction of about 2 logs of lymphoma cells (p=0.0021), but the majority of patients (77%) remained MRD positive. R-CHOP removed lymphoma cells more efficiently (>2 logs) inducing frequent molecular remissions (MR) in 76% (p<0.0001). This effect persisted within the first year after induction with 8/16 CHOP and 33/36 R-CHOP patients remaining MRD- after the first year (p=0.0016). Achievement of MR after induction correlated with improved progression free survival (PFS) in 54 evaluable patients (2-yr. PFS 60% in 19 MRD+ and 90% in 26 MRD- p=0.0133). MRD assessment maintained its prognostic significance when measured 1 yr. after induction, response duration (RD) was significantly longer in patients with MR after ASCT (n=30, RD 100% vs. 60%, p=0,0059) or IFN (n=30, RD 55% vs. 15%, p=0,0041). Evaluation of outcome according to postinduction MRD status and postremission treatment demonstrated that ASCT induces an improved PFS compared to IFN maintenance in 28 MRD+ patients (90% vs. 32% at 32 months p=0,0039) as well as in 30 MRD- patients (100% vs. 65% at 32 months)

Conclusions: Achievement of MR no matter by which treatment is of high prognostic relevance and can be used as surrogate marker for clinical outcome of patients with FL. ASCT as early consolidation improves outcome and MRD status may reveal patients that are potentially cured.

327 VALIDATION, REVISION AND EXTENSION OF THE FOLLICULAR LYMPHOMA INTERNATIONAL PROGNOSTIC INDEX (FLIPI) IN A POPULATION-BASED SETTING

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Introduction/background: The aim of this study was to validate the Follicular Lymphoma International Prognostic Index (FLIPI) in a population based cohort; and to study the relevance of revision and extension of the FLIPI with other prognostic variables.

Material and methods: Data of 353 unselected follicular lymphoma patients registered in the Eindhoven Cancer Registry were collected. Follow-up was completed up to January 1st, 2006. For efficiency and to avoid potential bias, we used multiple imputations for missing covariates. Validity was assessed by comparing observed to predicted survival of the original model and of a revised model with other prognostic variables. Discrimination was indicated by a concordance statistic.

Results: The original FLIPI stratified our cohort into three different risk groups based on stage (I-II/III-IV), Hb level (>7.3/<7.3), LDH level (normal/elevated), nodal involvement (0-4 sites/>4 sites), and age (<60/60+ years). The discrimination between risk groups was not as good as in the original cohort (c-stat=0.66). A model including age in three categories (<60/60-70/70+ years) and cardiovascular disease (yes/no) resulted in a better prognostic index (c-stat=0.70). The 5 year overall survival rates of this modified FLIPI low-, intermediate- and high-risk group were 79%, 59%, 28% compared to 81%, 66%, 47% for the original FLIPI.

Conclusions: The performance of the FLIPI was validated in a population-based setting, but can be significantly improved by a more refined coding of age (<60/60-70/70+) and by including the presence of cardiovascular disease. This modified FLIPI should therefore be considered as a basis for treatment decisions in follicular lymphoma patients in the general health care environment.

328 FOLLICULAR NON-HODGKIN LYMPHOMA GRADE 3A AND 3B SUBTYPES HAVE SIMILAR OUTCOME AND APPEAR INCURABLE WITH ANTHRACYCLINE-BASED THERAPY

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Background: Significant controversy persists regarding the clinical behavior of follicular lymphoma (FL) grade 3 and the relevance of subclassification into 3a and 3b subtypes. Studies have yielded conflicting results regarding the relative aggressiveness of these subtypes and their potential curability with anthracycline-based therapy. The aim of this study was to characterize baseline clinical features and survival outcomes among patients with FL3a and FL3b treated in British Columbia (BC).

Patients: 123 patients with FL grade 3 diagnosed between 1982 and 2007 and with pathology available for central review were identified using the Lymphoid Cancer Database of the BC Cancer Agency. Cases were designated as FL3a (n=108) or FL3b (n=15) by WHO criteria, excluding those with a diffuse component, which were designated as composite lymphoma.

Results: Median age of the entire cohort was 64 years (range 28-86). The proportion of patients with high-intermediate or high risk IPI scores was higher among FL3b (40%) than FL3a patients (17%), but did not reach statistical significance (p=0.22). An anthracycline-based regimen was received as initial therapy in 32% of FL3a cases and in 87% of FL3b cases (p <0.001); approximately one-third of patients in both subgroups received rituximab as part of their initial treatment. Median follow-up was 40 months (range 1-213). Comparison of disease-specific and overall survival revealed no significant difference between FL3a and FL3b subgroups, and no survival curve plateau was seen in either subgroup. 5-year overall survival (73% *v* 61%) and median overall survival (10.3 *v* 8.0 years) were similar between the FL3a and FL3b subgroups (p=0.94). Overall survival analysis limited to the FL3a cohort showed no difference between those who received an initial anthracycline-based regimen and those who did not.

Conclusions: Our data do not indicate any significant difference in clinical behaviour between FL3a and FL3b, and call into question the potential curability of either of these subtypes with anthracycline-based therapy. Additional cases are awaited for pathology review and molecular analyses are underway to further explore these preliminary findings.

329 IMMUNOCHEMOTHERAPY (R-MCP) PROLONGS SURVIVAL IN ADVANCED FOLLICULAR LYMPHOMA - 50 MONTHS UP-DATE OF A PHASE III STUDY OF THE EAST GERMAN STUDY GROUP HEMATOLOGY AND ONCOLOGY (OSHO#39)

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Introduction: We report the 50-months-follow-up data of our phase III trial comparing MCP - chemotherapy vs Rituximab + MCP both followed by interferon maintenance in advanced symptomatic follicular lymphoma.

Methods: Previously untreated patients with advanced stage, symptomatic CD 20-positive indolent NHL and mantle cell lymphoma (n=358) were randomized to receive either MCP-chemotherapy (mitoxantrone 8 mg/m^2 d1+2, chlorambucil 3x3 mg/m^2 d 1-5, prednisolone 25 mg/m^2 d 1-5 x 8 q 4 weeks) or MCP + Rituximab (375 mg/m^2 d -1). Here we report the results of the follicular lymphoma patients (grade 1+2), who represented the majority of patients and for whom the sample size was calculated, so this is not a subgroup analysis. Study endpoints included overall and complete response rate (RR + CR), progression free survival (PFS), event free survival (EFS), time to next treatment (TTNT), overall survival (OS) and toxicities.

Results: median follow – up of 50 months. Concerning toxicities there was no striking difference.

For the FL – ITT population the results are as follows:

	R-MCP (n=105)	MCP (n=96)	p-value
Response rate	92%	75%	.0004
Complete response	50%	25%	.0009
PFS median	NR	29 mo	<.0001
PFS 50 mo	68%	36%	
EFS median	NR	25 mo	<.0001
EFS 50 mo	66%	31%	
TTNT median	NR	28 mo	.0002
No retreatment at 50 mo	60%	32%	
OS median	NR	NR	.0205
OS 50 mo	86%	74%	

Conclusions: Concerning all end points Rituximab plus MCP is significantly superior to MCP alone. After a median follow-up of 50 months we can demonstrate asignificant survival advantage for the immunochemotherapy. At the 10th ICML up dated results will be provided.

330 THE ADDITION OF RITUXIMAB TO FRONTLINE CHOP SIGNIFICANTLY IMPROVES TIME TO TREATMENT FAILURE AND RESPONSE DURATION IN ALL FLIPI RISK GROUPS OF PATIENTS WITH ADVANCED-STAGE FOLLICULAR LYMPHOMA: RESULTS OF A RANDOMIZED TRIAL OF THE GERMAN LOW-GRADE LYMPHOMA STUDY GROUP.

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Background: The addition of rituximab to frontline chemotherapy has been shown to improve response rates, response duration and time to treatment failure in advanced stage follicular lymphoma patients. We asked whether this benefit is seen in patient subgroups of different prognoses, as defined by the recently developed follicular lymphoma international prognostic index (FLIPI).

Methods: The data of a randomized GLSG trial recruiting advanced stage follicular lymphoma patients, who were in need of therapy, from May 2000 to August 2003 were used to compare overall response rates (ORR), time to treatment failure (TTF), and response duration (RD) after CHOP versus R-CHOP induction therapy according to FLIPI risk groups.

Results: Of 566 evaluable patients, 70 (12%) patients were classified as low risk (LR), 241 (43%) as intermediate risk (IR), and 255 (45%) as high risk (HR) according to FLIPI. Overall response rates for R-CHOP vs. CHOP were 97% vs. 87% (p=0.16) in the LR group, 97% vs. 92% (p=0.08) in the IR group and 96% vs. 91% (p=0.13) in the HR group. With a median follow-up of 4.3 years, the 5-years TTF was 83% vs. 43% (median not reached vs. 3.9 years, p = 0.0019) in the LR group, 74% vs. 38% (median not reached vs. 3.4 years, p<0.0001) in the IR group, and 50% vs. 20% (median 5.0 vs. 2.3 years, p<0.0001) in the HR group. The 5-years RD was 86% vs. 50% (median not reached vs. 3.8 years, p = 0.0093) in the LR group, 76% vs. 39% (median not reached vs. 3.4 years, p<0.0001) in the IR group, and 52% vs. 22% (median 5.0 vs. 2.3 years, p<0.0001) in the HR group.

Conclusions: The benefit of rituximab was clearly observed in all FLIPI risk groups justifying the use of combined immuno-chemotherapy in all patients with advanced stage follicular lymphoma in need of therapy.

331 PHASE 3 RANDOMIZED FIRST-LINE INDOLENT TRIAL (FIT) OF CONSOLIDATION OF FIRST REMISSION WITH ^{90}Y-IBRITUMOMAB TIUXETAN (ZEVALIN) IN ADVANCED FOLLICULAR NON-HODGKIN'S LYMPHOMA (FL)

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Background: We conducted an international, prospective, controlled, randomized phase 3 trial to evaluate the efficacy and safety of consolidation with Zevalin (Zev) radioimmunotherapy in patients with advanced FL.

Methods: Major eligibility criteria: CD20$^+$ grade 1 or 2 FL, stage III/IV at diagnosis, normal peripheral blood cell counts, <25% bone marrow involvement, and CR/CRu or PR after first-line induction therapy. After induction, patients were randomized to either Zev (250 mg/m^2 rituximab on day -7 and day 0 followed on day 0 by Zev 0.4 mCi/kg; max 32 mCi) or no further treatment (control). The primary end point was progression-free survival (PFS), calculated from time of randomization.

Results: 414 patients (Zev, n=208; control, n=206) were enrolled at 77 centers. Patient demographics and induction therapies were well balanced between treatment arms. After Zev consolidation, 77% of patients in PR after induction converted to CR. Median PFS data (in months) after a median observation time of 3.5 years are provided below. As expected, toxicity was primarily hematologic; details will be discussed.

	N	Zev PFS, mo	N	Control PFS, mo	HR	95% CI	*P* value
All patients	208	37	206	13	0.465	0.357, 0.605	<0.0001
Response status after induction							
PR	101	29	97	6	0.304	0.213, 0.434	<0.0001
CR	107	54	109	29.5	0.613	0.410, 0.914	=0.0154
FLIPI scores							
Low	56	not reached	62	24	0.599	0.357, 1.006	=0.0502
Intermediate	58	54	54	11	0.227	0.134, 0.385	<0.0001
High	36	24	30	6.5	0.587	0.322, 1.070	=0.0789

Conclusions: Consolidation of first remission with Zev in patients with advanced FL resulted in high PR to CR conversion rates regardless of type of first-line induction treatment, prolonged PFS by 2 years overall, and extended PFS in all FLIPI subgroups.

332 LONG-TERM FOLLOW-UP OF PATIENTS TREATED WITH TOSITUMOMAB AND ^{131}I TOSITUMOMAB (BEXXAR^{TM})

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Introduction: Between March 1996 and July 2001, 100 patients (pts.) with recurrent/refractory B-cell NHL received BEXXAR^{TM} according to standard methodology, either in consecutive phase II trials, or on a compassionate basis. Long-term follow-up data are reported.

Patients: At the time of therapy, the median age was 52 years (yrs, range 27-90); 42 pts had bone marrow involvement (all <25%). Histology: follicular lymphoma (FL) 88, biopsy-proven transformation to diffuse large B-cell lymphoma having occurred in 20, mantle cell lymphoma 5, lymphoplasmacytoid 5 and small lymphocytic lymphoma 2. Treatment was given a median of 3½ yrs from diagnosis (1 mo-20½ yrs) and after a median of 2 prior therapies (1-15), including high-dose therapy in 11 (receiving an attenuated whole body radiation dose of 45 cGy). Twenty-five pts had failed to respond to their last therapy and 10 were refractory to rituximab. All pts are included in the analysis (4 received only the dosimetric dose; 3 disease progression,1 developed human anti-mouse antibodies).

Results: The overall response rate was 62% (33% achieving CR/CRu). Median duration of response was 1.4 yrs (95% CI: 0.8-5), with a plateau observed from 5 yrs at 34%. Median progression-free survival was 7 mos (95% CI: 6 mo -1yr), median overall survival (OS)3 yrs from therapy (95% CI: 2.2-5.8) and 6¼ yrs (95% CI: 5 – not reached [NR]) for responders. Those achieving CR/CR(u) had a significantly better OS (median not reached [NR]), 65% at 5 yrs), than those in PR (median 2 yrs [95%CI: 1.9-5.4], p<0.000). Pts treated at 1st or 2nd recurrence had a superior OS (median 5½ yrs [95% CI: 3yrs-NR]) than those treated later (median 2yrs [95% CI: 7mo-4¾ yrs]). Transformation was associated with a worse prognosis than persistent FL (median OS 10 mos [95% CI: 2mos-2¾ yrs] compared to 5 yrs [95% CI: 1.2-2.9] P=0.002). One case of tMDS has been reported at 4.5 yrs.

Conclusion: These results, with a minimum follow-up of 6 yrs confirm the durability of CR/CRu in pts treated at recurrence of FL with Bexxar.

333 ELDERLY PATIENTS WITH UNTREATED ADVANCED STAGE FOLLICULAR LYMPHOMA (FL) TREATED WITH BRIEF CHEMOIMMUNOTHERAPY RITUXIMAB® FND+/-RITUXIMAB MAINTENANCE: PRELIMINARY ANALYSIS OF A PROSPECTIVE RANDOMIZED STUDY

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Introduction: we investigated efficacy and safety of a brief chemo-immunotherapy RFND followed by randomization between R maintenance or observation in a study specifically devised for elderly.

Material and methods: From January 2004 to December 2007, 235 pts (age 60-75) with untreated advanced stage FL were enrolled and treated with: 4 courses of RFND (Fludarabine, Mitoxantrone, Dexamethasone) followed by 4 weekly R consolidation; CR+CRu+PR pts were randomized between R maintenance (375 mg/m^2 every months for 4 doses) or observation. PCR analysis for IgH/Bcl-2 rearrangement was performed on bone marrow (BM) at diagnosis, after RFND, R consolidation and during maintenance/observation. Preliminary analysis was done after the first 80 randomized pts. This analysis included 95 pts recruited within this time frame.

Results: Median age 65 (60-75); stage III/IV 16/70%; FLIPI low(L) 10%, intermediate(I) 30%, high(H) 60%. PCR analysis was done in 91 pts at diagnosis: 56% were Bcl-2+.

	N	ORR	CR	PCR negativity associated with CR(46 pts Bcl2+ evaluable)
Baseline	95	–	–	–
R-FND x 4	95	86 (90%)	51 (54%)	18 (39%)
R consolidation	88	80 (84%)	68 (72%)	31 (67%)

Univariate analysis was performed: high CR rate was achieved also in poor prognosis pts (CR according to FLIPI: L 75%, I 88%, H 81%). The most frequent CTC grade 3-4 toxicity was neutropenia in 25% of the courses, with only 6 serious infections. No toxic deaths occurred. Any grade R related reactions were seen in 9% of the courses with R discontinuation in only 2 pts. So far 91 pts are alive and 4 died of lymphoma.

Conclusions: A brief chemo-immunotherapy RFND + R consolidation is safe and effective with a high CR rate and PCR negativity in elderly pts with untreated FL with FLIPI H. R consolidation convirted in CR 56% of PR after RFND. The whole study will provide insights on the role of R maintenance after R-chemotherapy.

334 PENTOSTATIN COMBINED WITH CYCLOPHOSPHAMIDE, AND RITUXIMAB (PCR) ACHIEVE HIGH RESPONSE RATES IN INDOLENT B-CELL LYMPHOMA

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Background: The addition of rituximab to combination chemotherapy has improved treatment outcomes of indolent lymphomas. Combination therapy with purine analogs, akylating agents, and monoclonal antibodies is a promising approach for treating indolent B-cell lymphoma. Nucleoside analog-based regimens selectively target lymphoid cells, making them attractive drugs for lymphoid cancers. Pentostatin is a nucleoside analog that compared with other nucleoside analogs appears to have less bone marrow cell toxicity. The combination of pentostatin, cyclophosphamide, and rituximab (PCR) is an effective regimen for relapsed chronic lymphocytic leukemia and relapsed indolent B-cell lymphoma.

Methods: In this study, we examined the efficacy of pentostatin, cyclophosphamide, and rituximab for the treatment of B-cell lymphoma. Pentostatin (4 mg/m^2), cyclophosphamide (600 mg/m^2), and rituximab (375 mg/m^2) were given on day 1 of a 21-day cycle with planned 6 or 9 cycles and restaging after every 3 cycles. Patients received prophylaxis with acyclovir 400 mg/po bid and trimethoprim-sulfamethoxazole 3 times per week. Small lymphocytic lymphoma/chronic lymphocytic leukemia (SLL/CLL) tissues were stained for ZAP70 protein.

Results: At the time of abstract submission, 80 patients with a median age was 60 years completed therapy, 43 patients with follicular lymphoma, 27 with SLL/CLL, and 9 with mucosa-associated lymphoid tissue (MALT). Two patients with relapse lymphoma were treated. We observed an overall response of 77 out of 80 (96%), CR/CRu in 65 out of 80 (81%), PR in 12 out of 80 (15%), and mixed response or progression in 3 out of 80 (4%). Neutropenia (49% < 1000/uL), thrombocytopenia (2% < 100,000/uL), nausea (15% grade 3), fatigue (37% grade 3 and 4), and muscle pain (21% grade 3) was observed. ZAP70 staining and response will be reported. Two patients experienced prolonged pancytopenia that resolved and no cases of myelodysplasia were observed.

Conclusions: PCR therapy is an effective regimen in indolent B cell lymphoma with tolerable toxicity.

335 RANDOMIZED COMPARISON OF CLADRIBINE SINGLE (CDA) OR IN COMBINATION WITH CYCLOPHOSPHAMIDE (CCDA), AND COP IN PREVIOUSLY UNTREATED LOW GRADE B-CELL NON-HODGKIN LYMPHOMA PATIENTS - FINAL REPORT

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On Behalf on the Polish Lymphoma Research Group

Introduction: To comparatively assess first-line treatment with cladribine (CdA), CdA and cyclophosphamide (CCdA) or cyclophosphamide, vincristine and prednisone (COP), previously untreated patients (pts) with low grade non-Hodgkin lymphomas (LGNHL) were randomly allocated to receive six monthly courses of CdA, CCdA or COP.

Methods: End points were treatment response, progression free survival (PFS), overall survival (OS), and toxicity. From 1st of July 2000 to 30th of June 2005, 197 pts were randomized in 17 centers. Finally, 162 pts who completed scheduled chemotherapy and for whom all clinical data were available were analyzed for end points of the study.

Results: Compared to COP, CdA or CCdA induced higher probability of overall response (odds ratio [OR]=4.0, 95% confidence interval [CI] 1.7-9,3, p=.002, and OR=8.5 95%CI 3.2-22.7, p<.0001, respectively), complete remission (OR=5.8, 95%CI 1.8-18.5, p=.003, and OR=14, 95% CI 4.4-44, p<.0001, respectively), PFS (log-rank test, p<.0001) but not OS. After incorporating the International Prognostic Index (IPI) in multivariate analysis, treatment with CdA-containing regimens remained an independent prognostic factor for PFS (χ^2=35.94, hazard ratio [HR]=2.38, p<.0002). Incidences of infections were similar in the randomized groups, whereas CCdA but not CdA induced more frequent neutropenia (36% and 7%), anemia (10% and 0%), and thrombocytopenia (15% and 0%) compared to COP (p<.05 for each). This resulted in higher frequency of prolongation of intervals between CCdA and COP cycles (37.3% and 13.3%, p<.05) but dose reductions due to hematological or other toxicity didn't differ significantly in CdA (12%), CCdA (20.3%), and COP (6.6%) groups.

Conclusions: For pts with LGNHL, first-line CdA or CCdA regimens both provided similar treatment responses and acceptable toxicity, and better response rates than COP.

336 OUTCOME OF RELAPSED/REFRACTORY FOLLICULAR LYMPHOMA PATIENTS IN THE GELA/GOELAMS FL 2000 STUDY: INTEREST OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN OS

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In the FL2000 study, untreated high tumor burden FL pts (n=359) were randomly assigned to receive 12xCHVP (cyclophosphamide, adriamycin, etoposide and prednisolone) plus interferon-α2a (18 months) (Arm A) vs 6xCHVP with 6 x rituximab and interferon (18 months) (Arm B). The final analysis (ASH 2007) confirmed the superiority of Arm B. We analyzed the outcome of 178 relapsed/refractory pts: 63 pts progressed on therapy (refractory), 115 progressed or relapsed after completing their first line treatment (off therapy). 105 patients were initially randomized in Arm A. Median time from diagnosis to progression for responding pts (n=115) was 2.6 years (ranged from 1.4 to 5.7 years). Second line treatment (n=155) was left at investigator's discretion: cytarabine-based in 24 %, alkylating-based in 22%, anthracycline-based in 21%, fludarabine-based in 16% or other in 17%. Seventy pts did not received anti-CD20 containing regimen. Forty two pts underwent ASCT. After salvage therapy, 81 pts reached CR/CRu and 23 reached PR (data missing in 20%). After a median FU (from time of first progression) of 30.5 months, the 3- and 5-year PFS after first relapse estimates were 50% and 26%, respectively. The 3- and 5-year OS after first relapse estimates were 71% and 52%, respectively. According to the initial randomization arm, no difference in OS and PFS was observed. The 3-year OS was better for patients that progressed off therapy: 81% vs 54% (*p=0.0003*). Patients that received ASCT at this time had a significantly improved 3-year OS: 92% vs 58% (*p < 0.0001*) (analysis restricted to patients younger than 70 years). Similar results were observed considering PFS. This preliminary analysis demonstrates that ASCT improves OS and EFS of relapsed/refractory high risk FL pts.

337 SECONDARY MALIGNANCIES IMPAIRED SURVIVAL AFTER 1ST LINE PURGED AUTOLOGOUS TRANSPALNTATION FOR ADVANCED FOLLICULAR LYMPHOMA NINE YEARS FOLLOW-UP OF A RANDOMIZED GOELAMS TRIAL

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Background: First results of the GOELAMS study, comparing autologous stem cell transplantation (ASCT) and standard chemotherapy, showed an increased progression-free survival (PFS) in the high-dose chemotherapy arm, but no advantage of overall survival (OS) because of an excess of secondary malignancies. We report the updated results of this study.

Methods: Newly diagnosed follicular lymphoma (FL) were randomized between chemotherapy (cyclophosphamide, doxorubicin, teniposide, prednisone) associated with interferon or to high-dose therapy followed by purged ASCT conditioned with total body irradiation.

Results: 166/172 patients were evaluable. Compared to chemotherapy, the 9-year PFS is higher after ASCT (64% vs. 39%; p=0.004). No difference in OS appeared between the chemotherapy and ASCT groups (76% and 80%, respectively). On multivariate analysis, the ECOG performance status score and the number of affected nodal areas independently affected OS, whereas the ECOG score, the number of affected nodal areas and the treatment arm independently affected PFS. A significant difference in the PFS curves between ASCT and chemotherapy was observed only in the low FLIPI group. An excess of secondary malignancies (12 vs. 1) was observed in the ASCT group compared to the chemotherapy group.

Conclusions: The observation of a plateau curve for PFS suggests that a subgroup of patients, probably those with the lowest tumor burden might be cured by ASCT. Despite these results OS was not modified in the ASCT group due to the increase in secondary malignancies. These data discourage the use of purged ASCT associated with TBI as a 1st treatment for FL.

338 VERY LONG-TERM FOLLOW-UP OF AUTOLOGOUS STEM CELL TRANSPLANTATION IN FOLLICULAR LYMPHOMA: A RETROSPECTIVE SINGLE-INSTITUTION EXPERIENCE

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The natural history of follicular lymphoma (FL) is a succession of remissions and relapses. Autologous stem cell transplantation (ASCT) is one therapeutic option. To conclude about the interest of ASCT in this slow progressive disease, a long term follow-up is necessary. However, few clinical studies address this issue. Our study reports the long-term outcome of 80 patients suffering from FL who underwent ASCT in our institution.

Patients characteristics: Between 1989 and 2004, eighty patients with FL underwent ASCT. Forty-five patients were males, median age at diagnosis and the moment of ASCT was 45.71 years (27-62 years) and 48.08 years (28-64 years), respectively. Average time between diagnosis and ASCT was 53 months. ASCT was performed upfront for 37 patients, at first relapse for 35 patients and at a subsequent relapse for the others. Response prior to ASCT was obtained using a CHOP-like regime for 48 patients (60%) or an aracytine based regimen for 22 patients (27,5 %). Sixteen patients received Rituximab. The conditioning regimen was either TBI+cyclophosphamide (63 patients) or BEAM (17 patients).

Results: Response after ASCT was CR/CRu in 71 cases (88.8%), VGPR in 4 cases, refractory diseases in 3 cases (data missing in 2 cases). No patient died during the ASCT procedure. Thirty-four patients experienced relapse after ASCT including 8 patients with histologic transformation. Thirty-eight patients required other treatments following ASCT; 19 of them received a Rituximab-based therapy. Twelve patients died (including 7 histologic transformations and 3 AML/MDS). The median follow-up is 7.75 years. The median EFS was reached at 8.9 years. At three, five and seven years EFS was 82.8%, 70.3% and 61.7% and OS was 96%, 91.4% and 85.9% respectively. The median OS has not been reached.

Conclusion: Our study demonstrates that ASCT is a procedure which can prolonge EFS and OS in FL. A plateau appears on the EFS Kaplan-Meyer curve at 38.3% after 10.6 years. Prognostic factors for EFS and OS will be presented at the time of the meeting.

339 EFFICACY OF HIGH-DOSE SEQUENTIAL CHEMOTHERAPY AND AUTOGRAFT FOR TRANSFORMED NON HODGKIN'S B CELL LYMPHOMA: RESULTS OF A RETROSPECTIVE ANALYSIS FROM GITIL (GRUPPO ITALIANO TERAPIE INNOVATIVE NEI LINFOMI)

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Background: We analyzed a consecutive series of 66 pts with a confirmed diagnosis of transformed follicular lymphoma (TFL) registered at the GITIL centers from 1988 to 2004 and treated with high-dose squential (HDS) chemotherapy and autograft.

Methods: Biopsy-proven histological transformation (HT) in diffuse large B cell lymphoma was observed at diagnosis (n=24; 36%) or at relapse after a treatment for FL (n= 42; 64%). Patient characteristics: median age 51 yrs (range 33–66), stage I-II/III-IV 8/58, IPI score 0-1/≥2 28/38. HDS regimen included: i. 3 APO or 3 DHAP courses; ii. sequential administration of hd-CTX, hd-Ara-C, hd-Etoposide, with peripheral blood stem cell (PBSC) harvests following hd-CY and hd-Ara-C; iii. myeloablative regimen with hd-Mitoxantrone/L-Pam (n=28) or BEAM (n=28 pts who could not receive additional anthracycline), or TBI-PAM (n=3); iv. PBSC autograft; v. consolidation radiotherapy on bulky disease. From January 1999, hd-CTX and hd-Ara-C has been supplemented with Rituximab (RHDS; n=34).

Results: Overall 59 pts achieved a CR (89%), 1 patient responded partially and underwent allogeniec BMT, 6 pts died for PD while on therapy (9%). With a median follow-up of 67 mos (range 23-170), 42 pts are alive (63.6%), 24 pts relapsed and died for PD (n= 23) or toxicity (n= 1). Five-year event free survival (EFS) and overall survival (OS) are 53% and 64%, respectively. No significant differences in OS and EFS were observed between pts with HT at diagnosis or at relapse, with IPI O-1 vs IPI >2. Of note, pts treated with R-HDS showed an improved clinical outcome (OS: 76% vs. 50%; EFS: 68 vs. 37 respectively), with a large difference that did not reach statistical significance because of the limited number of pts.

Conclusion: Our data strongly suggest that HDS regimen, in particular when supplemented with rituximab (R-HDS) is a very effective regimen in transformed B cell lymphoma.

340 LONG TERM MOLECULAR REMISSIONS AFTER AUTOLOGOUS HEMATOPOIETIC STEM CELL TRANSPLANT IN FOLLICULAR LYMPHOMA

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Autologous stem cell transplant (ASCT) has been shown to be an effective treatment for first-line and relapsed follicular lymphomas (FL). The aim of this retrospective study was to determine the clinical and molecular outcome of patients with FL who received ASCT during a 12-year period. All patients, who underwent ASCT for first-line or relapsed FL between January 1992 and December 2004, were studied. Seventy-one patients, with a median age of 45 years and a median follow-up of 108 months, were analysed. Most of them belonged to the subtype grade 1 (57%), had a high tumor burden (50%), were treated in first-line (52%) and received an unpurged graft (58%). After an anthracyclin-based induction regimen, they received BCNU, Etoposide, Aracytine, Melphalan (BEAM in 58%) or Cyclophosphamide and total body irradiation (42%) as conditioning for the ASCT. Thirty-eight patients were alive, 24 without progression between 4 and 12 years; 31 patients were dead, 7 without progression. A total of 38 patients (55%) developed recurrent lymphoma. The progression-free (PFS) and the overall survival (OS) at 10 years were 33% and 47%, respectively and the molecular PFS at 10 years was 37%. There was an apparent plateau on the remission duration curve at 32% at 72 months and on the molecular remission duration curve at 37% at 80 months. A plateau on the OS curve seemed to emerge at 41% from the tenth year. Three patients developed a secondary neoplasm and two a secondary myelodysplastic syndrome. The 10-year non-relapse mortality (NRM) was 20%. This long follow-up study showed a plateau on the PFS and on the molecular PFS curves, suggesting that a selected group of patients might be cured by ASCT.

341 MYELOABLATIVE RADIOCHEMOTHERAPY FOLLOWED BY AUTOLOGOUS STEM CELL TRANSPLANTATION IN FIRST REMISSION PROLONGS RESPONSE DURATION OF PATIENTS WITH ADVANCED-STAGE FOLLICULAR LYMPHOMA IN FLIPI RISK GROUPS: RESULTS OF A RANDOMIZED TRIAL OF THE GERMAN LOW-GRADE LYMPHOMA STUDY GROUP

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Background: Myeloablative radiochemotherapy followed by autologous stem cell transplantation (ASCT) significantly prolongs response duration (RD) in advanced stage follicular lymphoma patients in first remission after conventional chemotherapy (Lenz et al. Blood 2004, Deconinck et al. Blood 2005). We now asked whether dose

intensive approaches such as ASCT in first remission would improve treatment outcome independent of the risk profile of the patients as recently defined by the follicular lymphoma international prognostic index (FLIPI).

Methods: We analyzed the data of a GLSG-trial recruiting from 1996 to 2000 randomly comparing response duration after ASCT vs. Interferon-a (IFN- a) maintenance in patients younger than 60 years. Randomized patients, who achieved at least a partial remission after CHOP or MCP induction and received postremission therapy according to randomization were evaluable for this analysis.

Results: Of the 254 evaluable patients 48 (19%) were classified as low risk (LR), 125 (49%) as intermediate risk, and 81 (32%) as high risk according to the FLIPI. With a median follow-up of 88 months, the 5-years RD after ASCT vs. IFN- a was 81% vs. 54% (median not reached vs. 88 months, p=0.091) in the LR group, 62% vs. 28% (median 114 vs. 23 months, p<0.0001) in the IR group, and 59% vs. 22% (median not reached vs. 13 months, p=0.0014) in the HR group.

Conclusions: ASCT significantly prolonged response duration in the IR and HR groups according to the FLIPI, and the same tendency was observed in LR group, which was very small due to the inclusion criteria of the trial. These data indicate that after conventional chemotherapy ASCT might add clinical benefit to all patients with advanced stage follicular lymphoma independent of their risk profile.

342 THE MERIT STUDY – AN ADDENDUM TO THE INTERNATIONAL RADIOIMMUNOTHERAPY REGISTRY

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Introduction/background: Although prognostic factors (PF) for conventional lymphoma therapy are known and used in clinical and scientific practice, the PF for radioimmunotherapy (RIT) have not been defined until now. As the mechanism of action of RIT differs significantly from that of chemotherapy, immunotherapy or percutaneous radiotherapy, it may well be, that other factors than those comprised by the conventional indices – possibly related to individual lesions – influence the outcome after RIT.

Material and methods: MERIT as an addendum to the International Registry of Radioimmunotherapy (IRR) includes the documentation of imaging findings in this registry along with an online archive for the respective FDG-PET and CT-image files. Based on these data, the MERIT study group centrally performs an evaluation of lymphoma lesions before and after RIT. Together with the clinical data documented in the IRR, the aim of the MERIT study is to identify patient and lesion specific prognostic factors for the RIT of follicular NHL. The MERIT study includes patients with follicular lymphoma (FL) and lesions measurable by imaging who receive RIT alone.

Results: CT and FDG-PET image data of the first patients with FL were already uploaded in an anonymized state and coregistered. Prelimilarily, twenty-five measurable lymphoma lesions were evaluated. Four months (mean) after RIT, 14/25 lesions had a metabolic remission in FDG-PET, 15/25 lesions a remission in size. In lesions >50x30 mm before RIT, no metabolic CR was observed. In 3/8 patients, responding and progressing lesions were seen simultaneously.

Conclusion: The web-based documentation and evaluation of FDG-PET and CT image data is feasible. The high rate of patients with responding and progressing lesion seen simultaneously will allow to evaluate not only patient specific but also lesion specific prognostic factors of RIT.

343 THE RIT NETWORK PROVIDES REAL LIFE CLINICAL DATA ON RADIOIMMUNOTHERAPY FOR LYMPHOMA: AN INTERNATIONAL REGISTRY FOR RADIOIMMUNOTHERAPY-TREATED PATIENTS

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The RIT-Network (RIT-N) is a web-based, international registry that collects real-world, observational data from radioimmunotherapy (RIT)-treated patients with malignant lymphoma from across the world. Each country involved in the registry has a nominated national chairman who is responsible for running the national registry. The objectives of the registry are to collate and analyse real-world data from RIT-treated patients (pts) to learn more about the optimal use of RIT and how it can benefit lymphoma pts. RIT-N was started in December 2006, data from 10 countries (Argentina, Austria, Germany, Italy, Poland,South Africa, South Korea, Spain, Switzerland, United Kingdom) are evaluable so far. Electronic or paper-based data capture is used nationally, data are then transferred into one central data base. In total, 494 pts were enrolled until 1/08, 238 have been completely documented. The median age, evaluable for 351 pts, is 58 years (range 23-86). The tumor stage is documented for 468 pts, 29 stage I, 65 stage II, 111 stage III, 257 stage IV, 3 with extranodal involvement, for 3 the tumor stage is not known. Histological subtypes are documented for 470 pts. 5 Burkitt lymphoma, 2 B-CLL, 70 DLBCL, 3 MALT, 302 FL, 10 lymphoplasmacytic lymphoma, 61 mantle cell lymphoma, 8 nodal marginal cell lymphoma, 2 splenic marginal cell lymphoma, 5 transformed FL and 1 unclassified lymphoma. Previous therapies break apart into 95 radiotherapies (alone), 310 chemotherapies (1-4 different Ctx 271 pts, 5-8 Ctx 35 pts, 9-12 Ctx 4 pts), 225 RIT and 44 transplantats. The RITwas performed 1st line in 83 pts, 2nd for 49 pts, 3rdand consecutive in 132 pts. Clinical practice and usage of RIT differs from the labelled indications and can be assessed reliably through this registry, enabling analyses of outcome and toxicity data beyond clinical trials. Further analyses and publications from the international registry will support the design of new clinicl trials and help to guide clinical practice.

344 TANDEM HD-CHEMOTHERAPY AND MYELOABLATIVE RADIOIMMUNOTHERAPY WITH 131I-ANTI-CD20 RITUXIMAB IN RELAPSED AND REFRACTORY B-CELL LYMPHOMA: FINAL RESULTS OF A PHASE II STUDY OF THE GERMAN RAIT STUDY GROUP

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Introduction: Radioimmunotherapy has been shown to be effective in CD20 + B-cell lymphomas. Both non-myeloablative as well as myeloablative regimens have been employed for low grade and high grade lymphomas with impressive response rates and remission durations. The Press group and our group published data on myeloablative 131I-anti-CD20 RAIT with high response rates and favourable long term survival especially in FL and transformed FL. Therefore, this treatment approach was studied in a phase II study within the German Radioimmunotherapy Group.

Methods: Patients were to receive R-Dexa-BEAM, followed by BEAM and HD-RAIT 2-6 months after BEAM. 131-J-Rituximab was administered with a maximum kidney and lung dose of 25 Gy.

Results: From 1/2003 to 12/2005 16 patients (pts) with relapsed (14) or refractory (2) B- cell lymphoma were included in the study. 4 pts with FLI°,II°; 4 pts with DLBCL (all early relapses); 6 pts with transformed FL; 1 pt with MCL and 1 pt with marginal zone lymphoma were treated with 1 (15 pts) or 2 cycles (1 pt) of R-Dexa-BEAM. 14/16 pts achieving SD (1), PR (6) or Cru (7) were treated with BEAM, 2 pts dropped out after DEXA - Beam (1 PD, 1 CR with subdural haematoma). After BEAM 9/14 not progressing pts without limiting toxicity (1 SD, 1 PR, 7 CR) received HD-RAIT, 5 pts were drop-outs (1 PD, 3 PR: 2 impaired DLCO, 1 pancytopenia; 1 Cru liver toxicity). After HD-RAIT 7/9 pts achieved a CR, 1pt a SD, 1 pt PR. Of all pts included in the study, 10/16 patients are alive for 21-51 months. After HD-RAIT, 7/9 pts are alive for 21-50 months. 2 pts after HD-RAIT died in CR, 1 of pneumonia (8 months after HD-RAIT) and 1 of interstitial lung disease (2 months after HD-RAIT). After HD-RAIT for FL I-III, 5/7 pts are alive and 4/7 in CCR.

Conclusion: Tandem HD-chemotherapy followed by myeloablative RAIT is a feasible and effective treatment modality for relapsed poor prognosis CD20+ B-NHL offering the potential for long term relapse free survival, especially for FL I-III.

345 A PROSPECTIVE PHASE II COMPARISON OF AUTOLOGOUS (ASCT) OR ALLOGENEIC (ALLOSCT) BLOOD STEM CELL TRANSPLANTATION FOR INDOLENT B-CELL NON-HODGKIN LYMPHOMA (NHL) USING RICE REINDUCTION, THEN HIGH DOSE FLUDARABINE AND BUSULFAN CONDITIONING.

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Introduction: A genetically-randomized, phase II study began in 2001 to compare stem cell source following uniform re-induction and novel high dose chemotherapy for indolent B-cell NHL.

Patients and Methods: Pts with mantle cell lymphoma (MCL) in 1st remission or 1st relapse, or other indolent B-cell NHL in 1st or 2nd relapse were eligible providing adequate organ function. Pts received RICE x1 (Rituximab, Ifosfamide, Carboplatin, Etoposide, with apheresis d29-31 if ASCT), then FluBu (Fludarabine 50 mg/m^2/d d-6 to -2, Busulfan 3.2 mg/kg/d IV d-5 to -2) and SCT d0. AlloSCT pts received ATG d-2 to 0, MTX and CSA.

Results: 68 pts aged 31-66 years (median 50) were accrued. Respective pt numbers for ASCT (n=36) and donor SCT (n=32; related=30, unrelated=1, syngeneic=1) were follicular (FL)=24 and 17, MCL=6 and 4, small lymphocytic=3 and 6, transformed=2 and 3, other NHL=1 and 2, while disease status was CR1=1 and 0, relapse1=17 and 15, relapse2=7 and 13, primary refractory=11 and 4. Following last chemotherapy (n=67) median event-free survival (EFS) was 10mo, and 5yr EFS was 1%. Response to RICE was CR/PR=69%. SD=23%, PD=8%. Pre-RICE, 20 ASCT pts had marrow involvement, decreasing to 3 post-RICE. 2 pts had NHL in autografts. A median of 4.7 (0-14.5) x10^6 autologous CD34+ cells/kg were collected post-RICE. Post-Allo/SynSCT,

grade 2-4 aGVHD occurred in 8 (25%), limited cGVHD in 7 (22%) and extensive cGVHD in 14 (44%) pts. Non-relapse mortality (NRM) at 100days was 0% and 6%, and at any time was 0% and 26% for ASCT and Allo/SynSCT, respectively. At 4yr median follow-up, projected 5yr outcomes (logrank p values) of ASCT vs Allo/SynSCT for relapse rate were 51% vs 32% (p=0.13), EFS 47% vs 51% (p=0.99), and overall survival (OS) 65% vs 59% (p=0.10), while for relapsed FL only (n=41) EFS was 49% vs 51% (p=0.94) and OS 86% vs 59% (p=0.038), respectively.

Conclusion: These data suggest RICE in-vivo purges autografts but mobilizes blood stem cells only moderately well. Using RICE-FluBu, ASCT and AlloSCT result in similar EFS and OS for relapsed/refractory indolent NHL.