Indolent NHL

418 FOLLICULAR LYMPHOMA, IMMUNOCYTOMA, AND MANTLE CELL LYMPHOMA: RANDOMIZED EVALUATION OF CURATIVE RADIOTHERAPY IN LIMITED STAGE NODAL DISEASE

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Background: Indolent lymphomas in early stage nodal disease can be treated effectively by radiotherapy (RT). In Follicular lymphoma grade I/II (FL), optimal target volumes are controverse: involved field (IF) RT risks out-field relapse, large field RT implies higher toxicity. In Immunocytoma (IC) and Mantle Cell lymphoma (MCL), experience is limited. This study aims to determine adequate age-adapted RT volumes in FL patients (pts) (randomised trial, RD) and to evaluate standardised RT in IC and MCL pts (prospective observation trial, OBS).

Methods: In FL stage I-II, limited stage III disease, pts aged 18-65 years (ys) were randomised to Extended field (EF) or Total lymphatic RT (TLI), basic dose 30 Gy + 10 Gy boost to macroscopic lymphoma. Pts aged 66-75 ys were treated by EF. In IC / MCL pts aged 18-75 ys stage I-II, modified EF RT was given. All pts >75 ys received IF RT.

Results: A total of 269 pts was recruited to the completed study. In the RD trial, 202 pts with FL were randomised to EF or TLI, median age 53 (23-65) ys; stage I, II and III were 57%, 34% and 9%. In the OBS trial, 67 pts, median age 70 (30-85) ys, were included, 54 with FL, 2 with IC, 11 with MCL. In the updated combined analysis of RD and OBS trials, overall survival is 96%, median follow-up 24 months. In FL, complete remissions (CR) were 179/191 (94%), relapses occurred in 37/179 pts (21%, median interval 21 months). In IC and MCL, 2/2 and 5/6pts reached CR, 1/2 and 4/5 relapsed. RL were strictly nodal (81%), combined with spleen and/or liver (10%), involved skin/soft tissue (7%) or were gastrointestinal (5%). In 74% of RL, histology was obtained: 12% of these were secondary aggressive lymphoma, 88% remained indolent.

Conclusions: In the randomised FL pts, EF and TLI induced high rates of CR. The analysis of relapse histology and patterns contributes to the definition of optimal irradiation volumes in early stage disease and provides the basis for further treatment improvements. In MCL, local therapy does not seem to be able to control the disease.

419 SAFETY AND EFFICACY OF RADIOIMMUNOTHERAPY WITH ^{90}Y-RITUXIMAB IN PATIENTS WITH RELAPSED OR REFRACTORY CD 20+ B CELL NON HODGKIN'S LYMPHOMA: A PILOT STUDY

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Background: Both anti-CD20 antibodies (ibritumomab; Zevalin® and tositumomab; Bexxar®) used in daily practice for radioimmunotherapy (RIT) of B cell NHL are murine immunoglobulins. The use of chimeric antibodies (such as rituximab) for radioimmunotherapy may potentially augment immune-based anti-tumour activity, improve pharmacokinetics, and reduce immunogenicity. The aim of this pilot single arm phase I-II study (in a single centre) is to evaluate the safety and efficacy of RIT with ^{90}Y-rituximab.

Materials and Methods: At present, 5 patients with B-cell non-Hodgkin's lymphoma (CD20+) in partial remission or progressive disease after at least 2 lines of therapy have been included in this study, with a follow-up of at least 3 months after therapy. We evaluated the safety and efficacy of RIT with ^{90}Y-rituximab, using the same doses and treatment schedule as actually approved by the European Medicines Agency for the treatment with ^{90}Y-ibritumomab tiuxetan (Zevalin®). Response assessment with ^{18}FDG-PET/CT was performed 3 months after the treatment and/or when progressive disease was clinically suspected.

Results: 3 patients had follicular lymphoma, 1 had mantle cell lymphoma and 1 diffuse large B cell lymphoma. Toxicities related to ^{90}Y-rituximab were mild (grade 2 or less) and primarily haematological with spontaneous recovery. Nadir blood counts occurred at to 6 weeks following therapy for platelets and at 8 to 9 weeks for white and red blood cells. Response assessment with ^{18}FDG-PET/CT at 3 months following treatment with ^{90}Y-rituximab showed a complete metabolic response in 3 out of 5 patients, one patient had minimal residual disease and one had progressive disease.

Conclusion: The preliminary results of this study suggest that radioimmunotherapy with ^{90}Y-rituximab in patients with relapsed CD20+ B-cell non-Hodgkin's lymphoma is safe, well tolerated and efficient when using the Zevalin® treatment schedule.

420 RADIOIMMUNOTHERAPY OF NEWLY DIAGNOSED, ADVANCED, LOW-GRADE LYMPHOMA WITH ^{131}I-RITUXIMAB: THE INITIAL STUDY

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Introduction: Radioimmunotherapy (RIT) with ^{131}I-labeled tositumomab has previously been shown to be safe and effective first-line therapy for low-grade Non Hodgkin lymphoma (NHL), with a CR of 75% and five-year PFS of 59%. We report a physician sponsored phase II trial of ^{131}I-rituximab RIT of previously untreated, advanced, low-grade NHL.

Methods: Eligibility criteria comprise CD20 +ve low-grade NHL, ECOG status 0-2 and adequate haematopoietic function (neutrophils $> 1.0 \times 10^9$/L, platelets $> 70 \times 10^9$/L, Hb >100g/L) and no prior NHL treatment. Administered therapeutic activities of ^{131}I-rituximab limited the whole body absorbed radiation dose to 0.75 Gy.

Results: To date 23 patients have been enrolled; 3 are awaiting treatment. 20 patients have follicular NHL, 2 have lymphoplasmacytoid lymphoma and one low-grade NHL (NS). The median FLIPI score for patients with follicular NHL was 3. Disease assessment by PET-CT scan at three months showed an ORR of 92% with a CR of 62%. Haematological toxicity was minimal with a mean neutrophil nadir of 1.39×10^9/L at week 7 and a mean platelet nadir of 89×10^9/L at week 4. One patient experienced grade 4 haematological toxicity requiring a single prophylactic platelet transfusion. There were no episodes of neutropenic sepsis and no renal or hepatic toxicity. Seven patients were assessable at 12 months; 4 of 5 patients in CR at 3 months remained in CR. Both patients with a PR at 3 months had progressive disease, although only one has required subsequent chemotherapy. Both of these patients had a baseline FLIPI score of 4.

Conclusion: ^{131}I rituximab radioimmunotherapy is safe and effective as first-line therapy for advanced low grade lymphoma. The achievement of a CR on PET-CT criteria at three months confers an excellent prognosis at 12 months.

421 QUALITY OF LIFE (QOL) ANALYSIS FROM THE PHASE 3 RANDOMIZED FIRST-LINE INDOLENT TRIAL (FIT) IN PATIENTS WITH ADVANCED-STAGE FOLLICULAR LYMPHOMA RECEIVING CONSOLIDATION OF FIRST REMISSION WITH ^{90}Y-IBRITUMOMAB TIUXETAN (ZEVALIN)

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Background: The QoL impact of consolidation therapy with Zevalin (Zev) compared with no further treatment (control) was evaluated as one of the secondary end points of the recent international phase 3 FIT study.

Methods: Health-related QoL was measured using EORTC QLQ-C30 (version 2), which specifically assesses QoL in patients with cancer, and EuroQoL-5D (EQ-5D), a generic instrument to assess health-related QoL that includes a visual analogue scale (VAS). Questionnaires were administered at screening, week 14, every 6 months thereafter, and at the final follow-up visit. Descriptive statistics were used to compare scores across treatment groups. The change in scores from baseline was also assessed by gender, age, and first-line treatment.

Results: Mean scores for EQ-5D and VAS at screening and final visits are shown in the Table. An exploratory analysis of factors associated with final VAS scores showed that only baseline VAS scores affected final VAS scores (P<0.0001). No treatment differences were observed in EORTC QLQ-C30 (all domains) scores across time points or changes from baseline. Results of subgroup analyses by baseline characteristics will be presented.

	Zev screening	Zev final	Control screening	Control final
EQ-5D	0.83	0.84	0.84	0.83
VAS	77.52	77.64	76.57	78.60

Conclusions: Health-related QoL parameters were similar between patients receiving consolidation with Zev and patients receiving no further treatment, as measured by EORTC QLQ-C30 and EQ-5D questionnaires. In patients with advanced-stage follicular lymphoma in first remission, treatment with Zev consolidation is efficacious while maintaining QoL.

422 HIGH RESPONSE RATES FOR STAGE 1-II INDOLENT B-CELL LYMPHOMA WITH YTTRIUM-90 IBRITUMOMAB TIUXETAN (ZEVALIN)

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Background: Yttrium-90 (^{90}Y) ibritumomab tiuxetan (Zevalin) is an effective treatment for patients with relapsed follicular lymphoma. There is no standard treatment for stage I and stage II indolent lymphoma.

Methods: Patients with CD20-positive lymphomas, including follicular lymphoma grades 1 to 2 and marginal zone B-cell lymphoma of the mucosal associated lymphoproliferative tissue (MALT) were included. Staging was calculated via computer tomography (CT) scanning of the neck, thorax, abdomen, and pelvis, PET/CT scanning, and bone marrow biopsy. Eligibility criteria were a performance status of 2 or less, a white blood count greater than 1500/mL, a platelet count greater than 100,000/mL, and at least one lesion measuring 1.5 cm in the transverse dimension. Response evaluation of bowel disease required repeat biopsies of involved tissues after therapy was completed. Patients were treated with rituximab and Zevalin (0.4 mCi ^{90}Y/kg capped at 32 mCi) at day 8 following the imaging dose on day 1.

Results: Ten patients who had completed therapy and were evaluable for response had a median age of 58 y (range: 36–76 y), with five male, 7 having follicular lymphoma, and 3 having marginal zone lymphoma. Ten patients have had follow-ups of at least 3 months and 9 of 10 have achieved a CR (1 patient has stable disease in a site of a recent surgical procedure). Patients experienced a median platelet count nadir of 50,000 (range: 20,000–170,000), at 4 weeks and a neutrophyl count nadir of 1,323 (range: 560–1,566). There were no neutropenia-related infections. Nonhematologic toxicity included a rash associated with Rituximab/^{90}Y ibritumomab tiuxetan administration.

Conclusions: Yttrium-90 ibritumomab tiuxetan is a highly active therapy that is completed in 8 days for early stage follicular and marginal zone B-cell lymphoma with minimal toxicity.

423 90-YTTRIUM-IBRITUMOMAB TIUXETAN CONSOLIDATION FOLLOWING 3 CYCLES OF FC-R IN ELDERLY PATIENTS WITH RELAPSED LYMPHOMA: A DOSE-FINDING STUDY

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Background: Fludarabine-based Tx followed by Y-90 ibritumomab tiuxetan (RIT) consolidation may improve PFS in patients (pts) with CD20+ NHL. 4 to 6 cycles of FC-R and then RIT at standard activity lead to severe prolonged pancytopenia. Briefer chemoimmunotherapy and RIT at lower Y-90 activity may alleviate this problem.

Methods: Rituximab-/anthracycline-pretreated pts unsuitable for autotransplant received 3 cycles of FC-R. If ≥ stable disease was achieved and blood counts normalised, RIT was given. Y-90 activity levels were predefined at 11/15 MBq/kg. 1st endpoint was the rate of dose-limiting toxic events (DLT) induced by RIT per level of Y-90 activity. 1 DLT in two cohorts of 3 pts per level was acceptable. DLT was defined as grade 4 neutropenia or thrombocytopenia for >14 days or non-hem toxicity of > grade 2 for >7 days.

Results: 22 pts entered the trial (10 follicular, 10 mantle cell, 2 other). Median age was 69 years. Median no. of pre-Tx was 1.9 pts went off treatment before RIT due to persistent cytopenia or progression. 13 received RIT. Nadirs occurred at median 7 weeks post-RIT. Median ANC nadir was 0.6/nl, with 1 pt in the 11 and 2 in the 15 MBq activity level sustaining DLT neutropenia. Median PLT nadir was 37/nl. Grade 4 thrombocytopenia was found in 1 pt at each level but did not require transfusion. Only 3 pts had thrombocytopenia > grade 1 at week 12. Non-hem toxicity was rare and < grade 3. At med. 19 months follow-up in RIT-treated pts, only 1 in SD and 2 in PR before RIT have progressed.

Conclusions: RIT delivered after 3 cycles of FC-R at Y-90 activity of 15 MBq/kg may induce more severe neutropenia than at lower activity. Nevertheless, the incidence of infections, transfusions, hospital admissions and late cytopenias is low. RIT at standard activity may be regarded safe in this setting. The long PFS observed may either be due to selection bias or the result of consolidation RIT.

424 REGISTRY OF RADIOIMMUNOTHERAPY: ANALYSIS OF OUTCOMES OF RECURRENT OR REFRACTORY NON-HODGKIN LYMPHOMA PATIENTS TREATED WITH 90Y IBRITUMOMAB TIUXETAN

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Background: The aim of this registry is to collect data of Non-Hodgkin Lymphoma patients (p) treated with 90Y-Ibritumomab tiuxetan in the clinical practice setting, to retrospectively analyze treatment outcome.

Methods: Endpoints analyzed: objective response rate (ORR), time to progression (TTP) overall survival (OS) and safety. Clinical prognostic factors were also studied.

Results: 169 p from 51 centres (treated since commercial availability in Spain and Portugal until August 2007) were registered: M/F 57.7%/42.3%; mean age 59.6 years (19-83); ECOG 0-1 79.7%; 113 had FL (66.9%) and 56 non-FL (33.1%). ORR was 66.9% (95%CI:59.8, 74.0). Median follow-up time was 6.6 months; median TTP, 10.1 months (95%CI:6.8, 13.3) and median OS has not been achieved. Estimated OS at 1 and 2 years: 74.1% and 51.0%, respectively. Intermediate and high FLIPI score were significantly associated with worse response rate and more risk for progression than lower score: Odds Ratio 0.29 (95%CI:0.09-0.88) and 0.25 (95%CI:0.08-0.77), respectively; Hazard Ratio 3.01 (95%CI:1.36-6.66) and 4.33 (95%CI:1.98-9.49), respectively. More than 2 previous treatments was also related with a worse response rate for FL p: Odds Ratio 2.49 (95%CI:0.87-7.08). Interventions required were: hospitalization 26.6%, G-CSF 43.8%, red blood cell/platelet transfusion 29.0/30.8%. Toxicity analysis is summarized in Table 1.

Table 1

Toxicity %(G3-4%)	
Anemia	56.2(23.7)
Neutropenia	62.7(45.6)
Leucopenia	67.5(37.3)
Thrombocitopenia	85.2(50.3)
Febrile Neutropenia	10.1(10.1)
Asthenia	36.1(8.3)

Conclusions: Despite the limitations of the retrospective design of the Registry, these results obtained with 90Y-RIT for lymphoma patients treated within the clinical practice setting are similar to that obtained in clinical trials. Updated data will be presented at the meeting.

425 MAINTENANCE THERAPY IN FOLLICULAR NON HODGKIN LYMPHOMA: EXPERIENCE WITH 6 MONTHS RITUXIMAB BASED SCHEDULE

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Follicular non-Hodgkin's lymphoma (F-NHL) is rarely curable with standard chemotherapy, the natural history of disease is characterized by successive relapses. The addition of Rituximab to different chemotherapy regimens increases the response rate and progression-free survival (PFS), without significantly increase of toxicity. The administration of Rituximab as maintenance therapy is an useful and safe option for patients in complete remission after induction therapy with regimens based in immuno-chemotherapy, nevertheless the best maintenance schedule is not yet defined.

Objective: To present our experience with an homogeneous maintenance schedule with Rituximab administrate every 6 months for F-NHL.

Patients and methods: Prospective, observational study in 41 F-NHL patients in complete remission after first line therapy with immuno-chemotherapy (R-CHOP, R-FC, R-MCF) since January 2002 to July 2006. Maintenance schedule: Rituximab 375 mg/m2 weekly × 4 every 6 months two years in an outpatient protocol of fast infusion (24 hours before the patient received anti H1 and H2 orally and steroids 40 mg, dexclorfeniramina 5mg and paracetamol 1 g IV previously to administration every Rituximab dose in a total volume of 250 mL. The first 50 mL is administered in 30 and 200 mL in 60 minutes), patients with severe previous reactions were excluded of this schedule and received Rituximab in slow infusion. Patients were evaluated previous to start maintenance and two months after 4 courses, CT scan, PET and molecular study of t(14;18) in bone marrow were performed. Side effects according to common toxicity criteria were evaluated. Overall survival and relapsed free survival were analyzed according Kaplan-Meier and Cox regression study.

Results: 37 valuable patients (25 F/12 M); Mean age 53.1(35-77). ECOG 0(60.8%), 1(34.7%), 2(4.3%); At diagnosis: B symptoms 43.4%; FLIPI 0(8.1%), 1(43.4%), 2(30.4%), 3(17.3%); stage I(8.6%), II(17.3%), III (39.1%), IV(34.7%); grade I(43.5%), II(56.5%); Bulky 14%; extra node disease 14%; Hb<10 g/dL (14%); LDH increased 14%; B2M increased 14%. R-CHOP (69.5%), R-CHOP+local Rx (8.7%), R-FCM (17.3%), R-FC (4.3%). 90% of patients have received maintenance fast infusion

protocol. Adverse events 2 patients (8.6%) had mild skin erythema during infusion, 2 (8.6%) previously treated with Fludarabine+Rituximab developed neutropenia grade 3-4: Overall survival mean 29.2 months (95% CI:12-63), RFS: mean 24 months (95% CI:6-55). Only two patients have relapsed, one of them with loss of CD20 expression in 70% of B malignant cells.

Conclusions: Rituximab maintenance therapy in outpatient protocol of fast infusion could be a good strategy to prolong RFS in F-NHL, the tolerance is acceptable and satisfactory in most of the patients. It is necessary a longer follow-up to consider the magnitude of the effect obtained.

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426 TWENTY YEARS FOLLOW-UP OF CHOP VERSUS CHLORAMBUCIL (CHL) IN INDOLENT LYMPHOMAS: A PRE-RITUXIMAB RANDOMIZED TRIAL FROM THE DANISH LYFO STUDY GROUP

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Background: Indolent lymphomas are characterized by a chronic course with a median survival of 7–10 years. Very long-term follow-up data are needed, but rarely available. We here present long-term results from a randomized trial conducted in the period 1983–1989 by the Danish LYFO Study Group comparing CHOP with CHL in patients with advanced stage indolent lymphoma.

Material and methods: 146 patients with indolent lymphoma were randomized to either 9 cycles of CHOP (4 weeks intervals) or CHL (10 mg daily for 6 weeks, followed by 2 mg daily for 9 months). Patients were originally diagnosed according to the Kiel classification: CC/CB follicular 69%, CB follicular 1%, CC/CB diffuse 15%, small lymphocytic 12%, and unclassifiable low-grade 3%. Median age (range) was slightly lower for the CHOP as compared to the CHL cohort, 51.5 (29-76 yrs) and 58.5 years (34–78yrs), respectively, (p=0.12). Male gender was 50% vs 38%, (p=0.15), and stage IV disease 69% vs 62%, (p=0.39). Histological subtype, nodal vs extranodal disease, B-symptoms, LDH, and performance score were all equally distributed.

Results: The data table shows event free (EFS) and overall survival (OS).

Treatment arm/end point	5 years	10 years	15 years	20 years
CHOP (EFS %)	37	26	17	12
CHL (EFS %)	26	17	12	11
CHOP (OS %)	71	46	33	21
CHL (OS %)	57	37	24	18

No statistical differences between the two groups were found in terms of EFS or OS.

Conclusion: In the pre-rituximab era, more intensive combination chemotherapy (CHOP) was not superior to oral monotherapy with regard to EFS or long-term OS.

427 PHASE I DOSE ESCALATION STUDY OF FLUDARABINE, BORTEZOMIB, AND RITUXIMAB FOR RELAPSED/REFRACTORY INDOLENT AND MANTLE CELL NON-HODGKIN LYMPHOMA

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Background: Fludarabine (F) and bortezomib (B) have both demonstrated tolerability and efficacy in patients (pts) with non-Hodgkin lymphoma (NHL). Despite potential synergy between these agents, the combination remains untested.

Methods: Pts with relapsed/refractory indolent and mantle cell NHL and were eligible. Dose levels of F and B were escalated as below with rituximab (R) being added to cohort 5. Due to unanticipated hematologic toxicity at dose level 5, 5a and 5b were added. Cycles were repeated every 21 days for a maximum of 8 cycles.

Results: 23 pts have been enrolled to date. Patient histologies include 12 with follicular, 4 with marginal zone, 3 with lymphoplasmacytic, 2 with small lymphocytic, and 2 with mantle cell NHL. No dose limiting toxicities were observed in cohorts 1 through 4. The addition of R in cohort 5 resulted in dose limiting hematologic toxicity. At dose levels 5a and 5b, no further grade 3 or 4 hematologic toxicity has been observed with cycle 1.Of the 17 pts currently evaluable for a response, 3 have achieved a CR, 4 have achieved a PR, 8 had stable disease, and 2 pts progressed on therapy. The median time of stable disease for the 8 pts was 9 months (range 3-30+).

Conclusions: FBR is a well-tolerated and active regimen for pts with relapsed or refractory NHL.R may worsen the hematologic toxicity of a nucleoside analog and proteasome inhibitor containing regimen.

Level	Fludarabine (25 mg/m^2)	Bortezomib (mg/m^2 on days 1,4,8,11)	Rituximab (mg/m^2 on d1)
1	d1-3	0.7	–
2	d1-3	1.0	–
3	d1-3	1.3	–
4	d1-5	1.3	–
5	d1-5	1.3	375
5a	d1-3	1.0	375
5b	d1-3	1.3	375

428 BENDAMUSTINE/MABTHERA IN PATIENTS WITH RELAPSED OR REFRACTORY AGGRESSIVE CD20+ B- CELL-LYMPHOMA (OSHO #73)

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Introduction: Bendamustine has been extensively studied in patients with indolent B cell neoplasms showing high response rates and moderate mostly hematologic toxicity. However, only one small study of patients with relapsed non-Hodgkin's lymphomas (NHL) treated with bendamustine as a single agent has been published to date showing a response rate of approximately 40%. To further improve treatment results we initiated the following study.

Patients and methods: Adult patients (≥18 years) with relapsed or refractory aggressive CD20+ NHL, who had received at least one anthracycline based combination chemotherapy were eligible. The first course included mabthera 375 mg/m^2 on days 1,8,15 and 22 and bendamustine 60 mg/m^2 on days 1,8 and 15 of a 4 week cycle. Bendamustine 60 mg/m^2 days 1, 8 and 15 was given in cycles 2-4.

Results: Twelve patients aged 56 to 78 years (mean age 69.6 years) were included in this study. 10 patients had received one, 2 had had 2 prior therapies. 10 patients and 35 treatment courses are evaluable for response so far. Four patients had a complete, three a partial and one a minimal response. The overall response rate was 80%. Three of four patients are still in CR after 33, 18 and 6 months, respectively. One patient with a complete response had progressive disease after 2 months. Partial remission lasted for 2, 4 and 6 months in 3 patients. Two patients with high dose chemotherapy with autologous stem cell transplantation as first-line treatment had progressive disease after 1 and 2 courses, respectively. There was only one grade 3 leukopenia in one of 35 treatment courses and no further grade 3 or 4 hematologic toxicities. There were no toxicity-related treatment delays, interruptions or mortalities.

Conclusion: These preliminary results show that bendamustine/mabthera is a well tolerated regime with promising response rates also in patients with aggressive NHL. Larger patient numbers are needed to confirm our findings.

429 BENDAMUSTIN (B) AND RITUXIMAB (R) IN THE TREATMENT OF RELAPSED INDOLENT CD 20+ NON-HODGKIN- LYMPHOMA– A PHASE II STUDY OF THE EAST GERMAN STUDY GROUP OF HAEMATOLOGY AND ONCOLOGY (OSHO #072)

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Background: Promising results have been observed in several studies evaluating the combination of B plus R in patients with relapsed/refractory indolent lymphomas. Overall response rates (ORR) of 93%, including a 64% rate of complete remissions (CR) could be observed.

Material and methods: This prospective, non-randomized multicenter phase II trial was initiated in June 2004. As induction therapy patients with relapsed/refractory (besides Bendamustine-refractory) CD20+ B-cell-Lymphoma or mantle cell lymphomas were treated with Rituximab 375 mg/m^2 (day 1) plus Bendamustin 90 mg/m^2 (day 1+2) for up to 6 cycles. Patients with CR or PR after at most 6 cycles were recruited for a consolidation treatment. The consolidation therapy consisted of R 375 mg/m^2, bimonthly for maximal 4 infusions. The primary endpoint is event-free survival (EFS), secondary endpoints remission rate (CR+PR), toxicity, overall survival (OS).

Results: In this first interim analysis after enrolement of 48 patients, 40 patients finished the induction protocol. The median follow up is 19 months. Histologies included follicular (25), MCL (10), LPIC (8), and marginal zone (3) lymphoma.

Median age was 69 years (47-85). Patients had received one (34), two (11) or three (3) prior treatment regimes. After induction chemotherapy the ORR in this primary analysis population was 85%, including 42.5% CR, 42.5% PR, and 2% SD. The median EFS was 9 months (0-39), the median PFS 12 months (0.5-39), and the median OS 14 months (0.5-40). The primary hematologic toxicity was reversible myelosuppression; grade 3 / 4 hematologic side effects included leukopenia (16%), thrombocytopenia (5%), and anemia (1.4%).

Conclusion: BR was effective in the treatment of relapsed NHL achieving high remission rates and PFS for about 1 year. Furthermore, safety data indicate that B toxicities are manageable and the drug is well tolerated even in elderly patients. Updated results concerning the induction and consolidation therapy will be available for the meeting.

430 SAFETY IN PATIENTS RECEIVING MAINTENANCE RITUXIMAB (MABTHERA®) IN FOLLICULAR LYMPHOMA: RESULTS FROM THE PHASE IIIB MAXIMA TRIAL

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Background: The benefit of improved PFS for rituximab (R) maintenance in follicular lymphoma (FL) has been first reported by Hainsworth et al. and was later confirmed in randomized trials by Ghielmini, van Oers, and others. The primary objective of the current study is to extend the safety database for rituximab maintenance following a wide range of induction therapies.

Methods: The sample size of this trial was calculated to detect at least one rare event with an incidence of 0.32% with 80% power. Patients with FL having achieved a CR or PR after R-containing induction therapy were eligible to receive standard-dose R every 8 weeks for up to 2 years. Primary endpoint is safety, with standard secondary efficacy endpoints.

Results: 349 patients with FL have been enrolled at clinical cut-off for whom demographic data is available: Median age of the patient population is 56 years. 76% had their first lymphoma treatment prior to enrollment, while the remaining 24% had up to 4 previous treatments; 74% entered the study in CR/CRu. Data on a total of 809 infusions was available. Except for one patient who received R at standard infusion speed and suffered from a TIA no SAEs were recorded within 24h of the maitenance infusion, including those patients who received R via rapid infusion. Nine SAEs were recorded, all but one were considered unrelated. One patient with previously known cardiac arrythmias died 13 days after the 4th infusion of unknown causes. After clinical cut-off, another patient died of progressive lymphoma. Hematologic toxicity occured in 9 patients, with three grade 3/4 events (neutropenia), one resulting in febrile neutropenia. Data on efficacy will be presented.

Conclusions: R maintenance q 8 weeks in FL after rituximab containing induction therapy can be safely administered. Rapid-infusion appears to be safe in this setting.

431 COST OF FOLLICULAR LYMPHOMA (FL) IN MEDICARE PATIENTS

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Background: Over 10,000 cases of FL were diagnosed in 2007 in the United States. The direct medical costs attributable to FL are not clearly documented.

Methods: We analyzed the cost of FL using SEER-Medicare data. Patients had FL (by histology) as their first primary cancer diagnosed between 1998-2002 with follow up through 2005. Patients had to have ≥1 year of prior non-HMO Medicare coverage. Costs were taken from claims for inpatient, outpatient and physician services. Control comparisons were made both to the pre-diagnosis 12 month period and to a 5% sample of Medicare patients without a cancer diagnosis. Chemoimmunotherapy (CT) was classified based on agents used after diagnosis. Linear regression models were adjusted for age, co-morbidity score, diagnosis year, gender, and county of residence.

Results: There were 2,053 patients who met the inclusion criteria. The median time from diagnosis to first CT was 159 days. The most common CT regimens included CHOP±R (32%) and rituximab alone (25%) and CVP±R (18%). The unadjusted mean monthly cost was similar compared to both control groups (>$3,000). This cost declined over time but did not reach the pre-diagnosis level. After adjustment the incremental cost of FL was $3,202/month for the first year compared to the 5% Medicare sample ($p<0.05$). Increasing age, male gender, and Black race were significantly associated with increased monthly costs ($p<0.05$).

Conclusions: FL is associated with increased costs of care in the Medicare population, particularly in the first year after diagnosis where it is over $36,000 per patient.

Mean monthly cost ($) relative to diagnosis date

Health Service	12 Months Before	12 Months After	12-24 Months After	24-36 Months After	Medicare 5% Sample
Inpatient facility	230	2030	799	792	227
Provider	167	1507	732	1024	134
Outpatient facility	16	35	22	29	5

432 REMARKABLE PROGNOSTIC VALUE AND CONTRIBUTION IN STAGING OF F-18-FDG-POSITRON EMISSION TOMOGRAPHY IN FOLLICULAR LYMPHOMA

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Introduction: F-18-fluorodeoxyglucose positron emission tomography (FDG-PET) is a powerful tool for the imaging of aggressive Non Hodgkin's lymphomas and Hodgkin's lymphoma. In contrast, there is relatively little data on FDG-PET in follicular lymphoma (FL) in spite of its high FDG uptake.

Methods: A retrospective analysis of 127 FDG-PET scans was performed among 100 patients with FL (93% grade I or II). FDG-PET was obtained at initial staging (n=56) and results were compared with conventional staging. Post-treatment scans (n=71, in 87% patients treated by conventional therapy) were compared with clinical follow-up.

Results: FDG-PET compared with CT and clinical examination showed more foci of involvement in 30/56 (55%) FL patients, less in 7/56, the same extension in 15/56 and 4 patients revealed discordant founds on PET or CT only ($p<0.001$). FDG-PET upstaged essentially FL in 15 patients (from stage 0-2 to 3-4). Including results of trephine biopsy the stage was substantially changed in 13/56 (23%) patients, which was projected into treatment strategy. Post-treatment PET-positive patients (11/71) had shorter progression free survival (9/11 relapsed in median of 6 months) compared with PET-negative patients (56/71), 9 of whom relapsed in median of 10 months, 47 of them remain in remission (median follow up 19 months) ($p<0.001$). All of remaining 4/71 patients with PET-positivity of undetermined significance (close to cut-off) are in long-term remission (median follow up 39 months).

Conclusions: Our results indicate that FDG-PET is accurate and reliable method for staging of FL. Post-treatment PET positive patients are likely to relapse prior to PET negative patients. Surprisingly, presented data are very similar to those observed in studies with aggressive lymphomas.

433 CLINICAL FEATURES AND OUTCOME OF FOLLICULAR LYMPHOMA PATIENTS WITH BONE MARROW INVOLVEMENT

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Background: Approximately 40-45% of patients (pts) with follicular lymphoma (FL) have bone marrow (BM) involvement. In some cases clusters of malignant cells are found next to trabeculae, in others – circulating malignant cells detectable on peripheral blood. The aim of study is to explore the clinical features and outcomes of pts FL with different types of BM involvement.

Methods: From 1985 to 2005, 65 pts FL with BM involvement were included in the study. In 35 pts (54%) the BM involvement was accompanied with clinical and hematological manifestation of leukemia, in 30 pts (46%) - malignant cells detected only by the morphological examination. The clinical parameters and treatment options were balanced between the two groups. There were 33 (51%) men and 32 (49%) women, median age 53 years (range 21-73). 30 pts (46%) had FL grade 1, 15 (32%) presented B symptoms, LDH was increased in 21 (32%), 33 pts (46%) had ECOG ≥2. According to FLIPI, 5 pts (8%) ranked in the low risk, 26 (40%) in intermediate and 34 (52%) in high risk category. 37 pts (57%) had widespread disease at diagnosis, including abdominal lymph nodes 45 (70%), liver 15 (23%) and spleen 22 (34%).

Results: The efficacy of the first-line treatment (R±CHOP, R±CVP) was poor: CR was achieved in 28 pts (43%), while 21 (32%) were resistant to chemotherapy. The 5-year DFS and PFS were 24% and 22% respectively. There were no significant difference in OS and DFS of pts with two different type of BM involvement (7-year OS 58% vs 62%, 5-year DFS 58% vs 50%). LDH elevation, hypoproteinaemia, abdominal mass and more than 5 lymph nodes sites involvement is significantly associated with unfavorable prognosis.

Conclusion: The two types of BM involvement, with or without symptoms of leukemia, occur equally, do not have prognostic significance in FL, but the BM failure at diagnosis is associated with widespread disease, poor efficacy of first-line therapy and high risk of relapse. The future studies of the FL with BM involvement can help to develop the optimal therapeutic approach to this group of patients.

434 INITIAL PROGNOSTIC PROFILE OF FOLLICULAR LYMPHOMA PATIENTS WITH POOR OUTCOME

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Background: Follicular lymphoma is the most common type of low grade Non Hodgkin Lymphoma and it accounts for about 30% of all NHL. All widely accepted prognostic indices such as Follicular Lymphoma International Prognostic Index (FLIPI) and Italian Lymphoma Intergroup (ILI) identify different risk groups of patients, but great heterogenity in the outcome within these groups is still present.

Methods: We have identified 25 pts treated at the Institute of Hematology from 2002 up to the end of 2007 who did have poor outcome. We have defined poor outcome as death within 5 years of diagnosis, stable or progressive disease on initial therapy, or relapsus within one year after the completion of initial treatment. FLIPI index was determinated for all the pts.

Results: The mean age was 57.04±9.94 yrs, range 37-71 (52% of pts were <60 yrs). Advanced clinical stadium (III or IV) was recorded in 22 pts (88%), 11 pts (44%) had anemia, 19 pts (76%) had ≥4 regions affected, 15 out of 25 pts (60%) had elevated LDH, and 17 pts (68%) had high risk according to FLIPI. There was no statistical significance regarding the age of patients, level of Hgb and LDH, and low/intermediate and high FLIPI. The advanced clinical stadium (p=0.0001) and the number of affected regions (p=0.009) did show statistical significance.

Conclusion: In our group of pts FLIPI did not show a prognostic significance in terms of outcome. Therefore, further subgrouping of pts using additional parameters seems to be necessary to identify pts with high risk of poor outcome.