Indolent lymphoma

**295 ANALYSIS OF PROGNOSTIC FACTORS IN 424 MALT LYMPHOMA PATIENTS TREATED IN THE IELSG-19 MULTICENTRE RANDOMISED STUDY**


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**Background:** The IELSG-19 randomized study comparing chlorambucil (C) alone versus the combination of C and rituximab (R) versus the sole R is the largest prospective randomized trial ever conducted in MALT lymphoma. Main contributors were the Italian Lymphoma Foundation, the GELA group, Cancer Research UK, the Catalan Hematology Group and the Oncology Institute of Southern Switzerland. All MALT lymphoma pts with localized disease at any extranodal site who did not respond or were not suitable for surgery (including H pylori-negative gastric lymphomas) or those who failed antibiotic therapy were eligible, as well as those with disseminated or multifocal MALT lymphoma. The present analysis refers to 424 evaluable pts.

**Methods:** Reported in 393 pts and was 0 in 297 of them (70%). According to the international prognostic index (IPI), 66 pts (17%) had intermediate-high risk and only 9 a high risk score (2%). B-symptoms were present in 43 of 294 pts (10.9%) and LDH levels were associated with diffuse large B-cell lymphomas (DLBCL) of the skin. In this study, we investigated the prevalence of Bb and Cp infections in cutaneous biopsies from 108 patients with PCL.

**Results:** Prevalence of Cp infection in PCL is similar to those reported in controls; Bb is not associated with lymphoma regression in 62% of pts. However, DOX failed to eradicate Cp infection in half of pts, with a negative impact on outcome. Studies aimed to improve antibiotic eradication and anti-lymphoma activity of DOX in OAML.

**Aims:** To define the prevalence of chlamydiae infections, to evaluate bacterial eradication and anti-lymphoma activity of DOX in OAML.

**Methods:** The IELSG #27 trial had two parts: A) therapeutic part and B) molecular part. Pts with stage-IEA OAML and measurable disease were enrolled in part A, and received DOX 100 mg bid for 21 days. Pts with other lymphomas, benign lesions or MZL not eligible for part A entered the part B where patients were treated following local practice.

**Conclusions:** Cp infection is a common in OAML at diagnosis. First-line DOX was associated with lymphoma regression in 62% of pts. However, DOX failed to eradicate Cp infection in half of pts, with a negative impact on outcome. Studies aimed to improve antibiotic efficacy are warranted.

**297 A PHASE II STUDY TO INVESTIGATE THE PREVALENCE OF INFECTIOUS AGENTS IN OCULAR ADNEXAE MARGINAL ZONE LYMPHOMA (OAML) AND THE EFFICACY OF ANTIBIOTIC THERAPY (IELSG#27 TRIAL)**

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**Background:** OAML is associated with Chlamydia psittaci (Cp) infection. Cp eradication with doxycycline (DOX) is followed by lymphoma regression in ~50% of patients (pts). Related studies were retrospective, with a single prospective trial mostly including pts with relapsed disease. This is the first prospective phase II trial addressing Cp prevalence and DOX activity in pts with newly diagnosed limited-stage OAML (NECT01010295).

**Aims:** To define the prevalence of chlamydiae infections, to evaluate bacterial eradication and anti-lymphoma activity of DOX in OAML.

**Methods:** The IELSG #27 trial had two parts: A) therapeutic part and B) molecular part. Pts with stage-IEA OAML and measurable disease were enrolled in part A, and received DOX 100 mg bid for 21 days. Pts with other lymphomas, benign lesions or MZL not eligible for part A entered the part B and were treated following local practice. Chlamydiae infections were evaluated on diagnostic biopsies by three PCR (TETR, OmpA, hsp60). The same PCRs were used on conjunctival swabs and peripheral blood mononuclear cells (PBMC) collected before and after (at 3 & 12 months) DOX to monitor bacterial eradication.

**Results:** From 2006 to 2010, 54 pts were enrolled. Prevalence data are available for 44 cases: Cp was detected in biopsy of 32% (86%) of 37 assessed OAML and in 4 of 7 non-MZL. All cases were negative for the other Chlamydiae.

Twenty-eight of the 34 OAML pts enrolled in part A were assessable for Cp eradication (positive PCR on pre-DOX swabs in 8, PBMC in one or both in 19). All pts completed DOX treatment. Thirteen pts (46%) achieved Cp eradication (negative PCR in post-DOX samples); Cp was detected again at one year of f-up in two of them.

**Conclusions:** Cp infection is common in OAML at diagnosis. First-line DOX was associated with lymphoma regression in 62% of pts. However, DOX failed to eradicate Cp infection in half of pts, with a negative impact on outcome. Studies aimed to improve antibiotic efficacy are warranted.

**298 A PHASE II STUDY OF LENALIDOMIDE IN PATIENTS WITH MALT-LYMPHOMA**

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**Background:** MALT lymphoma is among the more common lymphoma entities and shares certain features with multiple myeloma. In view of this and the activity of lenalidomide in various B-cell lymphomas we have initiated a phase II study to evaluate the efficacy of lenalidomide in patients with MALT-lymphoma.
Patients and Method: Patients with histologically verified advanced MALT-lymphoma (in case of gastric MALT-lymphoma with demonstrated refractoriness to HP eradication) were included in the study. Treatment consisted of lenalidomide 25 mg p.o. days 1 - 12 with a 7 day-break after each cycle for a maximum of 6 courses. Restaging was scheduled after 3 and 6 cycles.

Results: A total of 18 patients were included in the trial (10 female/8 male); 5 had gastric and 15 extragastric lymphoma (6 orbital, 4 pulmonary, 1 parotid, 1 intestinal and 1 subcutaneous). Currently, 12 patients are available (9 after 3 and 1 after 6 cycles): 2 patients have achieved a CR (one after 3 and one after 6 courses) and 9 a PR (8 with ongoing therapy, one after 6 courses) and one SD. Two patients withdrew consent after the first course (due to itching/skin toxicity and fatigue). One patient showed transformation to DLBCL after initial PR of gastric MALT-lymphoma. Side effects consisted of neutropenia (grade 3 in 2 patients) and thrombocytopenia (grade 3 in one patient), two episodes of pneumonia as well as pruritus and exanthema in 5 cases (necessitating hospitalization in one patient), fatigue (2 patients), mild nausea (2 patients) and mild conjunctivitis, cramps and asthenia in one patient each.

Conclusion: These preliminary data suggest activity of lenalidomide in MALT lymphoma with manageable toxicity. The final results of the study are awaited.

299 BENDAMUSTINE AND RITUXIMAB AS FIRST LINE TREATMENT FOR PATIENTS WITH MALT LYMPHOMA. AN INTERIM REPORT OF A PHASE 2 TRIAL IN SPAIN (GELTAMO 2008-001)

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Introduction: MALT lymphoma is a subtype of indolent lymphoma that is considered to arise from a B-lymphocyte that has developed under the influence of a chronic antigenic stimulus. The role of FDG PET-CT either at staging or to assess response after treatment might be of clinical concern. We aimed to evaluate the usefulness of PET-CT in predicting the outcome in a series of patients with FL.

Methods: Patients and Methods: Phase II trial (EUDRACT 2008-00725-39) carried out in Spain by the GELTAMO group in untreated patients with disseminated or multifocal MALT lymphoma or with localized gastric MALT refractory to HP eradication.

Treatment: Bendamustine (90 mg/m2 d1-2) and Rituximab (375 mg/m2 d1), every 28 days.

Background: Background: The role of FDG PET-CT either at staging or to assess response after treatment might be of clinical concern. We aimed to evaluate the usefulness of PET-CT in predicting the outcome in a series of patients with FL.

Patients and Methods: Patients and Methods: Phase II trial (EUDRACT 2008-00725-39) carried out in Spain by the GELTAMO group in untreated patients with disseminated or multifocal MALT lymphoma or with localized gastric MALT refractory to HP eradication.

Introduction: Bendamustine and Rituximab is an effective regimen for treating patients with MALT lymphoma, but it is also associated with grade 3/4 toxicity, mainly neutropenia and fatigue. We aimed to determine the impact of adverse events on the quality of life of patients treated with Bendamustine and Rituximab in this setting.

Results: A total of 18 patients were included in the trial (10 females/8 males; median age 66 years). At least 6 cycles were planned for each patient.Forty-three percent of patients reported grade 3/4 neutropenia, which was the most common adverse event. Fatigue was the second most common adverse event, reported by 55% of patients. Twenty-five percent of patients reported grade 3/4 fatigue. Six patients (33%) withdrew consent after the first course (due to itching/skin toxicity and fatigue). One patient showed transformation to DLBCL after initial PR of gastric MALT-lymphoma. Side effects consisted of neutropenia (grade 3 in 2 patients) and thrombocytopenia (grade 3 in one patient), two episodes of pneumonia as well as pruritus and exanthema in 5 cases (necessitating hospitalization in one patient), fatigue (2 patients), mild nausea (2 patients) and mild conjunctivitis, cramps and asthenia in one patient each.

Conclusion: These preliminary data suggest activity of lenalidomide in MALT lymphoma with manageable toxicity. The final results of the study are awaited.

301 ELEVATED PRETREATMENT SERUM CYTOKINES PREDICT DISEASE RELAPSE AND A POOR PROGNOSIS IN FOLLICULAR B-CELL NON-HODGKIN LYMPHOMA (FL) PATIENTS

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Introduction: The role of FDG PET-CT either at staging or to assess response after treatment might be of clinical concern. We aimed to evaluate the usefulness of PET-CT in predicting the outcome in a series of patients with FL.

Methods: Newly diagnosed FL patients prospectively had 30 serum cytokines measured pre-treatment using a multiplex ELISA. 400 non-lymphoma controls were used to establish normal cytokine ranges. Principal components analysis (PCA) was performed on the combined FL and control dataset to identify cytokine profiles.

Results: 211 FL patients were included. The median age was 60 years (range 24-94) and 54% were male. 73 (34%) patients were initially observed while 29 (14%) received rituximab alone and 109 (52%) received combination therapy. At a median follow-up of 49 months (range 1.3-86), 103 patients (48%) had relapsed and 19 patients had died (9%). Three cytokine profiles were determined based on PCA analyses. 115 FL patients (53%) had a normal cytokine profile similar to the general population of controls; 81 (37%) had a lymphoma specific cytokine profile associated with elevation of FL-2R, IL-12, CCL19 and CCL20, and 15% had a profile associated with a non-specific cytokine elevation. Patients with an abnormal cytokine profile (either lymphoma or non-specific) had a significantly worse event-free (HR=1.92, 95%CI:1.29-2.84, p=0.001) and overall survival (OS) (HR=1.90, 95%CI:1.29-2.84, p=0.003). When patients with grade 3b FL were excluded, the difference in terms of OS maintained (3-year OS: 89 vs. 58% for PET-CT negative vs. positive, respectively; p=0.003).

Conclusion: PET-CT before treatment is related to histological grade and proliferation. PET-CT after treatment could predict the outcome of the patients in terms of OS.
Introduction: FL is characterized by an indolent clinical behaviour. However, in a fraction of patients it transforms to a more aggressive histology, often with a rapid clinical course and shortened survival. Hence, prediction of the transformation risk is important for a risk adapted treatment strategy. The aim of the study was to identify clinicopathological parameters at diagnosis influencing occurrence of HT in patients with FL.

Materials and methods: 2554 FL cases diagnosed 1983-2009 were identified from LYFO. We defined HT as the conversion of FL grade I-II to grade III or of any FL to DLBCL. Of these, 108% had both biopsy-proven HT and an evaluable set of clinicopathological parameters required for inclusion in the study. Uni- and multivariate Cox-regression analysis was performed.

Results: The cohort (N=2554) had a median age of 60yrs (15-97yrs) with a M/F ratio of 0.85. For HT cases median age at diagnosis was 59yrs (28-85 yrs) and the M/F ratio 1.08. Of all FL cases analysed at diagnosis 20.6% had evaluable s-LDH. 65.7% disseminated disease (stage III-IV) and 32.4% presented with extranodal manifestations. Poor performance score (WHO 2-4) was found in 8% of cases and 24.7% experienced B-symptoms. At univariate level risk of HT was significantly increased by a high FLIPI score, extranodal localization and in particular by an elevated pretherapeutic s-LDH. Interestingly hypogammaglobulinemia also significantly predicted the risk of HT. In fact in multivariate analysis the three parameters that, despite being statistically interrelated, retained the strongest predictive value for subsequent HT were hypogammaglobulinemia (p<0.005 HR=2.05 (1.24-3.41)), elevated s-LDH (p<0.001 HR=2.09 (1.33-3.26)) and extranodal disease (p<0.001 HR=2.17 (1.44-3.26)). The simultaneous presence of two or more of these factors had additive predictive value for the HT endpoint.

Conclusion: Pretherapeutic presence of elevated s-LDH, extranodal disease and/or hypogammaglobulinemia in FL patients significantly impact the risk of subsequent HT.

303 EARLY STAGE FOLLICULAR LYMPHOMA: ROLE OF MOLECULAR MONITORING IN PATIENTS TREATED WITH LOCAL RADIOTHERAPY ± RITUXIMAB

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Background: Conventional treatment of stage I-II follicular lymphoma (FL) is local radiotherapy (RT), which allows eradication of the disease in about 50% of patients. Very few data are available on the role of anti-CD20 MoAb and of minimal residual disease (MRD) evaluation in this setting.

Methods: 41 consecutive patients with a confirmed diagnosis of stage I/II FL were investigated by PCR in order to identify the presence of Bc-2 rearranged cells in the bone marrow (BM) and/or peripheral blood (PB). All patients were treated with involved field RT (36 Gy). Subsequently, MRD was evaluated every 6 months.

Results: PCR analysis revealed Bc-2 rearranged cells in 24/41 patients (58.5%) at presentation. After irradiation of the sole site of the disease, Bc-2 rearranged cells disappeared in 15 of the 24 (62.5%) patients positive at baseline; in 8 (19.5%) MRD was positive, while 1 patient refused the test. After a median follow up of 50 months, 5 patients (12.2%) had a clinical relapse. MRD evaluation demonstrated that: 17/41 Bc-2 negative patients at the basal evaluation were not subsequently retested; only 1/17 patients had a clinical relapse (the new biopsy documented a mantle cell lymphoma).

Of the 15 patients positive at baseline and who became negative after RT, 3 have had a molecular relapse during the follow-up, leading in one case to an overt clinical relapse.

Of the 8 patients persistently Bc-2 positive after radiotherapy, 3 had a clinical relapse. Rituximab (357 mg/m² x 4) was administered to 5 patients with a persistently positive Bc-2 after RT: 3 of them became Bc-2 negative.

Discussion: Viable Bc-2+ cells can be demonstrated in the BM and/or PB of the majority of stage I-II FL patients (despite a negative BM biopsy). Irradiation of the sole nodal/extranodal disease sites allows disappearance of Bc-2+ cells in the majority of previously positive patients (62.5%). Pre-treatment Bc-2 BM and/or PB evaluation has a prognostic role: no clinical relapses were observed in Bc-2 negative cases at baseline except for one patient, relapsed as mantle cell. MRD evaluation has a prognostic role: among 32 Bc-2 negative patients after treatment, 2 relapses (6.2%) were observed (1 relapsed as mantle cell), while among 8 Bc-2 positive patients after treatment 3 relapses (37.5%) were observed.

Prognosis of early stage FL treated with local RT ± rituximab is excellent: only 5 patients have so far relapsed at a median follow up of 50 months.

304 FINAL RESULTS OF RITUXIMAB PLUS CHLORAMBUCIL COMBINATION IN NAIVE FOLLICULAR LYMPHOMA PATIENTS

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Background: Conventional treatment of stage I-II follicular lymphoma (FL) is local radiotherapy (RT), which allows eradication of the disease in about 50% of patients. Very few data are available on the role of anti-CD20 MoAb and of minimal residual disease (MRD) evaluation in this setting.

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Results: PCR analysis revealed Bc-2 rearranged cells in 24/41 patients (58.5%) at presentation. After irradiation of the sole site of the disease, Bc-2 rearranged cells disappeared in 15 of the 24 (62.5%) patients positive at baseline; in 8 (19.5%) MRD was positive, while 1 patient refused the test. After a median follow up of 50 months, 5 patients (12.2%) had a clinical relapse. MRD evaluation demonstrated that: 17/41 Bc-2 negative patients at the basal evaluation were not subsequently retested; only 1/17 patients had a clinical relapse (the new biopsy documented a mantle cell lymphoma).

Of the 15 patients positive at baseline and who became negative after RT, 3 have had a molecular relapse during the follow-up, leading in one case to an overt clinical relapse.

Discussion: Viable Bc-2+ cells can be demonstrated in the BM and/or PB of the majority of stage I-II FL patients (despite a negative BM biopsy). Irradiation of the sole nodal/extranodal disease sites allows disappearance of Bc-2+ cells in the majority of previously positive patients (62.5%). Pre-treatment Bc-2 BM and/or PB evaluation has a prognostic role: no clinical relapses were observed in Bc-2 negative cases at baseline except for one patient, relapsed as mantle cell. MRD evaluation has a prognostic role: among 32 Bc-2 negative patients after treatment, 2 relapses (6.2%) were observed (1 relapsed as mantle cell), while among 8 Bc-2 positive patients after treatment 3 relapses (37.5%) were observed.

Prognosis of early stage FL treated with local RT ± rituximab is excellent: only 5 patients have so far relapsed at a median follow up of 50 months.

305 BENDAMUSTINE FOR PATIENTS WITH INDOLENT LYMPHOMA – A SYSTEMATIC REVIEW AND META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS (RCT)

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Background: Survival of patients with indolent lymphoma has improved in the recent decade. While it is clear that the addition of rituximab to induction chemotherapy improves survival of these patients, it is unclear which is the best chemotherapy to combine with rituximab. None of the chemotherapy regimens that had been compared in randomized controlled trials, were superior in terms of overall survival (OS).

A number of RCTs have examined the benefit of bendamustine in patients with indolent lymphoma. Progression free survival (PFS) was similar or prolonged with bendamustine compared to other chemotherapy and an OS benefit has not been shown. In order to evaluate the effect of bendamustine on the OS of patients with indolent lymphoma we performed a systematic review and meta-analysis.

Methods: We included RCTs that compared bendamustine to other chemotherapy regimens for patients with indolent lymphoma. In December 2010 we searched The Cochrane Library, MEDLINE, LILACS, conference proceedings, and databases of ongoing trials. The primary outcome was all cause mortality. Relative risk (RR) for dichotomous data and hazard ratio (HR) for time to event data were estimated and pooled.

Results: We identified 4 trials, conducted between the years 1994 and 2010 randomizing 1251 patients. Studies characteristics are presented in Table.

Patients treated with bendamustine had an improved OS compared to controls, RR for death 0.80; 95% CI 0.67 - 0.97, P = 0. After excluding the trial with only CLL patients the RR is 0.82; 95% CI 0.67 - 0.97.

PFS was improved with bendamustine, HR 0.47; 95% CI 0.39 - 0.57. The rate of complete remission improved with bendamustine compared to controls, RR 2.31; 95% CI 1.07 - 4.96, random effects model, I²= 88%. The rate of grade 3/4 adverse events was unaffected RR 1.21; 95% CI 0.99 - 1.48.

Discussion: This meta-analysis shows for the first time that bendamustine improves OS and PFS of patients with indolent lymphoma and CLL compared to other chemotherapy. These results should be interpreted cautiously due to the wide clinical heterogeneity of patients and treatments. Further trials of a more homogenous group should be performed to explore the role of bendamustine in various lymphoproliferative neoplasms.
306 LENALIDOMIDE PLUS RITUXIMAB LEADS TO A HIGH RATE OF DURABLE RESPONSES IN PATIENTS WITH RELAPSED/REFRACTORY INDOLENT NON-HODGKIN’S LYMPHOMA

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Background: Although indolent non-Hodgkin’s lymphomas (iNHLs) are responsive to initial therapy, patients continue to experience a relapsing and progressive disease course and most remain incurable with current treatments. Lenalidomide is an immunomodulatory agent which enhances rituximab-mediated antibody-dependent cellular cytotoxicity. In preclinical models, combining lenalidomide and rituximab (R2) improved antitumor activity relative to either agent alone. Here we provide an update of the results from a phase 2 trial investigating clinical activity and safety of R2 in relapsed/refractory (r/r) patients with iNHL.

Material and Methods: Patients had r/r iNHL with measurable disease, 21 prior therapies, and ECOG Performance Status $2. Lenalidomide 25 mg/day was initially administered on days 1–21 of each 28-day cycle until disease progression, while rituximab 375 mg/m² IV was administered on day 15 of cycle 1, and repeated weekly for a total of 4 doses. A second 4-week course of rituximab was permitted after cycle 2 for patients achieving less than complete response (CR).

Conclusions: Of 2 the first 4 patients developed grade 3 tumor lysis syndrome, the protocol was amended to reduce the lenalidomide dose to 20 mg, with allopurinol prophylaxis. The primary end point was overall response rate (ORR). Secondary end points were response duration, overall survival, progression-free survival (PFS), and safety.

Results: Of the 21 enrolled patients, 16 had follicular lymphoma (FL). The median age was 60 years (50–95), median number of prior therapies was 3 (range 1–11), and 7/21 (33%) patients were rituximab-refractory. The median number of cycles received was 3 (range 2–7), and 15/21 (71%) patients received R2. The most common grade 1–3 adverse events were lymphopenia (25%), neutropenia (19%), fatigue (13%), and hypertension (19%). For the 18 evaluable patients, the ORR (at least partial response) was 78%, including 6 patients (33%) with CR. At a median follow-up of 9 months, median PFS was 13 months. Notably, the ORR in patients with FL was 86% (95% CI 74%–95%). A FcgRIIIa genotype data was available for 11 patients with FL: 1 patient had V/V, 6 patients were heterozygous (F/V), and 4 patients had F/F. The ORR was 100% in the V/V type, 100% in the V/F type, and 50% in the F/F type. Median PFS was 14.8 months in the V/F type and 9.3 months in the F/F type.

Conclusion: Our data suggest that the R2 combination has significant clinical activity without appreciable toxicity in patients with rel/r iNHL, and may overcome the previously reported lower activity of single-agent rituximab in patients with the low-affinity type FcgRIIIa receptor.

307 EFFICACY AND SAFETY OF BORTEZOMIB-PLUS-RITUXIMAB (VCR) VS RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED, R-NAÏVE/-SENSITIVE FOLLICULAR LYMPHOMA (FL): OUTCOME ACCORDING TO PRIOR THERAPY

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Introduction: FL pts typically receive multiple lines of therapy with decreasing efficacy over the course of their illness. Identification of agents with improved activity in pre-treated pts is an important goal. The phase 3 LYM3001 trial showed improvements in overall response and CR rates and PFS with VcR in R67 pts with relapsed FL. Here we report activity and safety by line of therapy and prior R.

Material and Methods: Pts with relapsed grade 1/2 FL were randomized to five 5-week cycles of VcR (V: 1.6 mg/m², d 1, 8, 15, 22; R: 375 mg/m², d 1, 8, 15, 22, cycle 1, and d 1, cycles 2-5; N=336 or 0 (N=340).

Results: 103/98 VcR/R pts had high-risk FL; median age was 61/60 yrs, 51%/43% were male, 76%/66% were Caucasian and 19%/30% Asian, 34%/33% had $3 prior lines, and 39%/41% had prior R. ORR was 59%/57% (p=0.002), CR/CRu rate was 13%/6% (p=0.145), and durable (2mo) response rate was 45%/26% (p=0.008) with VcR/R.

Conclusion: With high-risk FL treated with VcR had significantly higher response rates and longer PFS than pts receiving R alone, with greater clinical benefit than in the overall population; additional toxicity was acceptable and did not affect treatment feasibility.

309 BENDAMUSTIN (B) AND RITUXIMAB (R) IN THE TREATMENT OF RELAPSED INDOLENT CD20+ 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 reported 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. The recruitment was finished in June 2009. Patients with relapsed/refractory CD20+B-Cell-Lymphoma or mantle cell lymphomas got an induction therapy with Rituximab 375 mg/m² (day 1) plus Bendamustine 90 mg/m² (day 1+2) for up to 6 cycles. After 6 cycles patients with CR or PR were recruited for a consolidation treatment with Rituximab 375 mg/m², monthly for maximal 4 infusions.

Results: The consolidation started 8 weeks after the last cycle of the induction therapy. The primary endpoint was event-free survival (EFS). Secondary endpoints were the rate of remissions (CR+PR), toxicity, and overall survival (OS).

Results: In this interim analysis 62 of 63 enrolled patients were evaluable. All 62 patients finished the induction protocol.

The histological findings of the study were: follicular lymphoma (33), mantle cell lymphoma – MCL (15), LPIC (8), marginal zone (5) and not classified indolent (2)
lymphoma. Median age was 67 years (45-85). Patient’s history showed one (44), two (14) or three (5) prior treatment regimes. The overall response rate (ORR) was 83% after induction chemotherapy (44% CR, 39% PR). 13% of the patients reached a CR during the consolidation treatment after only a PR at the end of the induction therapy. CR rate was 57% after consolidation. Both median EFS and PFS were similar 41 months. The two-year-EFS was 58%. The two-year-OS was 77%. The observed hematologic toxicity was a reversible myelosuppression (WHO III/IV leucopenia 10%, thrombocytopenia (6%), and anemia (2%). Only a low number of non-hematological side effects was seen (WHO III/IV infections 1.2%).

Conclusion: BR is a highly effective protocol in the treatment of relapsed NHL regarding the remission rates and PFS for about 2 years. Furthermore, our data indicate that the toxicity of the investigated combination therapy is safely to manage. The treatment was well tolerated even in elderly patients. The treatment can be recommended for outpatient with relapsed low-grade lymphoma.

310 TIME TO NEXT ANTI-LYMPHOMA THERAPY (TTNT) AND TREATMENT-FREE INTERVAL (TFI) WITH BORTEZOMIB-RITUXIMAB (VcR) VS RITUXIMAB (R) IN PATIENTS (PTS) WITH RELAPSED FOLLICULAR LYMPHOMA (FL)


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Introduction: TTNT is an increasingly important endpoint in FL, and a good measure of clinical benefit of treatment. The phase 3 LYM3001 trial showed higher response rates and longer PFS with VcR vs R in pts with relapsed FL. We report analyses of TTNT and TFI, which were pre-defined endpoints in the trial.

Material and Methods: Pts with grade 1/2 FL were randomized to five 5-wk cycles of VcR (1.6 mg/m2 x 5 wks), R, R 150 mg/m2 every 3 cycles, or VcR 150 mg/m2 every 3 cycles plus 3 cycles of GM-CSF. In pts with PR after induction chemotherapy, pts received 5 cycles of VcR vs 3 cycles of R. For pts with CR after induction chemotherapy, pts received 5 cycles of VcR vs 3 cycles of R. Subgroup analyses were performed based on categorical factors (eg sex, age, stage).

Results: After a median follow-up of 33.9 mo, 181/336 (54%) VcR and 204/340 (59%) R pts had received subsequent therapy. Median TTNT (23.0 vs 16.6 mo, HR 0.799, p=0.024) and TFI (17.7 vs 13.0 mo) were longer with VcR vs R. Sensitivity analyses, excluding pts who discontinued due to adverse events, had peripheral neuropathy (PN) at any time, or had PN at progression, confirmed the TTNT benefit of VcR, which was not affected by VcR-related PN. Type/intensity of subsequent therapy were similar in each arm. Median TTNT/TFI were longer with VcR vs R in pts who were J Hofer, G. Fasoulis, M. Kouroumplis, T. Apostolidou, M. Panagiotopoulou, I. Achtelik, H. Ghesquieres, J. Seymour, F. Offner, P. Feugier, P. Brice, C. Hiaioun, G. Bollard, J. Catalano, F. Jacobs, L. Fidler, G. Sallek

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311 RITUXIMAB PLUS SARGRAMOSTIM FOR THE TREATMENT OF NEWLY DIAGNOSED FOLLICULAR LYMPHOMA: FINAL RESULTS OF A PHASE II STUDY

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Background: Rituximab (R) works in part through antibody dependent cellular cytotoxicity (ADCC). Several cytokines can enhance ADCC:Sargramostim (granulocyte macrophage-colony stimulating factor - GM-CSF) is an FDA-approved cytokine that stimulates the proliferation and differentiation of hematopoietic progenitor cells. In addition to stimulating multi-lineage hematopoietic recovery GM-CSF may augment dendritic cell numbers and promote antigen presentation. We and others (Cartren G, YUC 2008) have explored the combination of R + GM-CSF for patients (pts) with follicular lymphoma (FL). Following encouraging pilot experience (Liu N. ASH 2003) in 2006 we organized a multi-center trial of R + GM-CSF for pts with untreated FL.

Methods: Pts with untreated FL were eligible for study. R was administered at 375mg/m2 once weekly x 4 weeks plus GM-CSF, 250 µg sc three times weekly x 8 weeks. The planned sample size was 52 with a primary endpoint of complete response (CR) rate at 3 mo. Secondary end points included progression free survival (PFS) and safety of the combination. Response was assessed using the 1999 International Working Group Criteria.

Results: From 12/2006-5/2009, 52 pts enrolled and all were eligible for assessment. The median age was 56 (31–78) and 62% were male.56% of patients had intermediate or high risk FL.IPIL Fifteen (29%) pts had bulky disease (>5cm) and 29 (56%) pts had elevated LDH.Tolerance was good and effective attributable to GM-CSF and R. Absolute granulocyte count above 15K occurred in only 2 pts; conversely, ≥ grade 3 neutropenia occurred in 8 pts. No significant infections occurred. At 3 months, the overall response rate was 69%, including 23% of pts with a CR. With continued follow-up, response rates improved (CR 74%, CRv 49%). Remissions were seen in 46% of pts in remission without further treatment. At a median follow-up of 14 mo, the median PFS of all pts was 28 mo including pts with bulky disease (median PFS, 16 mo). No difference in PFS was observed when comparing FLIPPO score (0–1) vs (2–3) or BMI.

Conclusion: Rituximab plus GM-CSF is well tolerated and active in untreated pts with FL. There did not appear to be a significant difference in outcomes when comparing FLIPPO scores, although PFS was inferior in patients with bulky disease. Randomized studies are required to determine whether this combination is superior to rituximab as a single agent.

312 IMPACT OF RITUXIMAB MAINTENANCE TYPE AND FCGRIIA AND FCGRIII A GENOMIC PROFILE IN PATIENTS WITH PREVIOUSLY UNTREATED FOLLICULAR LYMPHOMA

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Background: The PRIMA study has shown that maintenance with Rituximab (R) during 2 years improve progress free survival in pts with previously untreated follicular lymphoma (FL) responding to immunochemo. Polymorphisms in the IgF receptor FcRgRllal and FcRgRil genes have been associated with response in several lymphoma types. The aim was to compare pts receiving R maintenance (RM) in pts with previously untreated FL responding to rituximab or immunochemotherapy and, also to analyse the impact of polymorphisms regarding progression free survival, incidence of hypogammaglobulinemia and Ig levels.

Patients and Methods: pts with FL in CR or PR after first-line R or R-Chemo received RM: type 1) R 375 mg/m2 every 3 or 2 months during 2 years. FcgRIIa and FcgRIIIa genotypes were determined by allele-specific PCR.

Results: 39 consecutive pts included. Characteristics: median age 66 ± 45 years; Ann Arbor III/IV: 85%; B-symptoms: 11%: FLIPPO 3 or more: 48%. Induction treatment: 15% chemom; 8% R and 77% R-Cemo. 66 pts received antracyclin-containing chemio. Status at starting RM: CR in 80% and PR in 20%. Type of RM: RM1 in 41% and RM2 59%. FcgRIIa HH 22%, HR 5% and RR 56%, and FcgRIIIa VV 28%, VF 54% and FF 8%. At a median follow-up of all RM of 40 months (3-106), 9 pts have relapsed and died. Overall and progression free survival at 4 years were 95% and 79%, respectively. Antracyclin-containing chemio was significantly associated with a different probability of progression (HR 5.2; 95% CI 1.1-25.1, p=0.022), but not the following variables: status prior to maintenance, type of maintenance and FcgRil or FcgRIllal genotype. Hypogammaglobulinemia was present in 41% and 49% of pts before and after RM, respectively. Levels of IgM diminished at the end of maintenance in pts with FcgRllal HR-RR (p=0.019) and in those with FcgRIllal VF-FF (p=0.017). IgG and IgM levels did not significantly change during maintenance.

Conclusions: RM for 2 years in pts with previously untreated follicular lymphoma (FL) responding to immunochemotherapy is a very active therapeutic strategy, especially in those pts receiving induction antracyclin-containing chemo. The two schedules of R maintenance were effective and all pts benefited independently of FcgRIllal and FcgRIllal genomic profile. Levels of IgM were significantly influenced according to FcgRIllal and FcgRIllal genotypes.
**314 RADIOIMMUNOTHERAPY (RIT) WITH 177LUTETIUM-DOTA-RITUXIMAB (177Lu-D-R): FINAL RESULTS OF A PHASE II/II STUDY IN 31 PATIENTS WITH RELAPING FOLLICULAR, MANTLE CELL AND OTHER INDOLENT B-CELL LYMPHOMAS**

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**Introduction:** 177Lutetium linked to the chimaeric anti-CD20 antibody rituximab (R) with DOTA as chelator emits beta-rays (0.497 MeV) and a gamma-component suitable for imaging. Handling is less hazardous than for 131I and the beta-component may provide a more favourable tumour/non-tumour ratio than 131I. Our aim was to determine the maximum tolerated dose (MTD) and to explore clinical response.

**Material and Methods:** From 02/02 to 05/09 31 pts were treated in 7 cohorts (m:17, f:14, median # of pretreatments (Tx): 3 [2-7], 22/31 had received R pre RIT). Tx consisted of R (250mg/m2) on d1 and d8. Pts were hospitalized for 5 days for imaging and, at higher doses, to fulfill irradiation safety requirements. Dose escalation was done in steps of 50mg/m2. Reassessment was on week 10.

**Results:** Toxicity: Gr II fatigue and Gr I nausea were reported on the days following Tx. Reassessment was on week 10. One brief Gr IV episode was seen in 1 of 5 pts at level 3 and in one pt at level 4. Gr II and Gr III neutropenia were observed. One Gr II at level 7. This pt succumbed to sepsis in neutropenia. Tc: One Gr III at levels 4-6 (nadir: wk 7) was observed. Further testing is warranted in follicular and MZL.

**Conclusions:** FCGRA SNP does not appear to influence the response rate after R-chemotherapy alone or followed by maintenance in this prospective study. Other SNPs possibly influencing R activity are currently being evaluated.

**315 AUTOLOGOUS STEM CELL TRANSPLANTATION WITH IMMUNOTHERAPY INDUCES PROLONGED CLINICAL AND MOLECULAR REMISSIONS IN MURINE PATIENTS WITH RECURRENT FOLLICULAR LYMPHOMA**

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**Introduction:** We hypothesized that the addition of immunotherapy to HDI/ASCT may augment "in vivo" graft purging and achieve more effective eradication of minimal residual disease (MRD) post ASCT. This may lead to improved PFS and OS.

**Methods:** We conducted 3 sequential IRB approved prospective phase 2 trials of HDI/ ASCT combined with immunotherapy in patients with relapsed FL from 1997-2010. Patients received either a interferon (a-IFN), Rituximab (R) or R+ a-IFN post ASCT. An in vivo purge of lymphoma cells from the stem collection was performed in trials 2 and 3 with one or three doses of R respectively during the stem cell mobilization.

**Results:** 13 pts are alive after a median of 84 mo (32-103). Four pts remain in remission without ASCT. Other lymphomas (n=4): One pt with marginal zone lymphoma died of recurrence 46 mo later. One pt with transformed FL progressed on 177Lu-D-R and died 46 mo later. One pt with a transformed FL was able to proceed to peripheral blood stem cell mobilization and ASCT. The high dose therapy regimen consisted of etoposide 60 mg/kg/day -4 and melphalan 180 mg/m2 day -3 +/- 1200 cGy TBI in 6 fractions with stem cell infusion day 0.

**Results:** The median age at transplantation was 64 (range 30-65) years, and the median time to transplantation was 3.4 years (range 0-22). 29 (26%) had prior rituximab exposure. Patients received a median of 2 salvage regimens for TRIL (range 0-4), 66% received an anthracycline, 78% received platinum, and 43% received rituximab. 47% proceeded with ASCT, and 53% did not because of progressive disease (n=40), inability to collect/mobilize stem cells (n=18), death due to toxicity of salvage chemotherapy (n=1) and other reasons including comorbidities (n=5). 5 yr OS for patients post ASCT were 45% and 40%, respectively. PFS was not influenced by the timing of ASCT for TRIL (part of first or second-line therapy, p=0.450) or the addition of rituximab to salvage (p=0.503). Those transplanted after 2004 had improved 3 yr OS (72% vs 59%, p=0.004) but differences in 3 yr PFS (54 vs 27%, p=0.054) were not statistically significant. Transplant-related mortality was 4%. Among non-transplanted patients, those with progressive disease had 5 yr OS of 6%, while those not transplanted...
for other reasons (n= 18) had 5 yr OS of 68%, which was similar to that of patients undergoing ASCT (p=0.253).

Conclusions: Ability to proceed to ASCT and outcomes after ASCT are consistent with results for other aggressive NHL. Outcomes following ASCT appear to have improved over the last 5 years, although the role of rituximab as part of salvage chemotherapy in this patient population requires further evaluation.

317 PRIMARY INTESTINAL FOLLICULAR LYMPHOMA: A SINGLE INSTITUTION STUDY OF 40 CASES IN THE RITUXIMAB ERA

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Background: Follicular lymphoma (FL) is the second common subtype of non-Hodgkin’s lymphomas in western countries and Japan. Primary intestinal follicular lymphoma (PIFL) is a relatively rare lymphoma. Recently, PIFL have been gradually well known among hematologists, gastrointestinal endoscopists, and pathologists, and have established new variant of FLs in the World Health Organization (WHO) classification 4th edition. We report the clinicopathological findings and outcome of PIFL in the rituximab era.

Patients and Methods: From September 2001 to June 2010, 40 patients (pts.) were diagnosed PIFL, and treated at the Cancer Institute Hospital, All the histopathology samples were reviewed according to the WHO classification by expert hematopathologists.

Results: Baseline pt. characteristics included a median age of 61 years (range, 46-78 years), 16 men and 24 women, 19 pts. (47.5%) with stage I (according to the International Workshop staging classification in Lugano 1993), four (10%) with stage II, four (10%) with stage III, and 13 (32.5%) with stage IV. Twenty-five pts. (62.5%) have low risk of original FLIPI, five (12.5%) have intermediate risk, and eight (20%) have high risk (two were not evaluated). Fourteen pts. (35%) have low risk of FLIPI2, nineteen (47.5%) have intermediate risk, and four (10%) have high risk (three were not evaluated). The most frequent site was the second portion of duodenum (67.5%) presenting as multiple small white granular polyps. Grade 1 and 2 of follicular lymphoma were 27 pts (67.5%) and seven (17.5%). Twenty-three pts. (57.5%) have received rituximab or rituximab containing chemotherapy included of 18 treated with rituximab maintenance therapy, and 12 (30%) have received localized radiation therapy. At a median follow-up of 43 months (range 7.5-113), the 4-year progression-free survival and overall survival rates were 78.9% and 92.9%, respectively. Seven pts were confirmed progression disease, and one died from progression of lymphoma, and another from acute myeloid leukemia.

Conclusions: We reconfirmed to characterize the clinicopathological features of the PIFL in the rituximab era. To date, endoscopic devices, such as double balloon enteroscopy and video capsule endoscopy are in progress for diagnosis of small intestinal involvement of lymphoma. Using of new endoscopic devices, the diagnosis of PIFL will increase in early stages. PIFL demonstrated excellent prognosis in the rituximab era.

318 PATTERN OF INFECTIONS OBSERVED DURING THE MAINTENANCE PHASE IN THE PRIMA STUDY

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Introduction: Efficacy of rituximab maintenance (RM) after immuno-chemotherapy induction in first line treatment of follicular lymphoma demonstrated a significant benefit on progression free survival in the PRIMA study (Selles et al., Lancet 2011). One of the critical aspects of this maintenance procedure is its harmlessness regarding the most frequent adverse event, i.e. infectious complications. We then examined in more details the characteristics of infections occurring in the PRIMA study.

Methods: Out of 1019 patients randomized in PRIMA study, 1009 patients were assessed for safety (508 in observation (OBS), 501 in RM); all reported AE/SAEs were examined.

Results: The most common AE were grade 2–4 infections in 197(39%) patients in the RM arm and 123 (24%) patients of the OBS arm, respectively (risk ratio 1.62, 1.35-1.96; p<0.0001). The five most common infections reported in the RM and OBS arms were bronchitis, upper respiratory tract infections, sinusitis, nasopharyngitis (in aggregate 114 and 61 cases, respectively) and urinary tract infections (14 and 9, respectively). The cumulative numbers of Herpes viruses-related infections were 19 and 12, respectively. Infectious AEs that occurred with a higher incidence (≥2% difference) in the RM arm were bronchitis (11% vs. 6%), upper respiratory tract infection (6% vs. 2%) and sinusitis (4% vs. 2%); only 1 and 2 febrile neutropenia episodes did occur. There were 26 (5%) AE considered as being serious related to infection in the RM arm vs. 6 (1%) in the OBS arm. The number of infections recorded at each rituximab cycle did not increase over time. There were no more infectious AE in patients below 65 years, between 65 to 74 years, over 75 years. The pathogens documented were usually common. Four patients in the RM arm discontinued treatment as a result of infections (2 hepatitis, 1 endocarditis, 1 mycobacterial infection). There were 2 fatal infections in the RM arm (1 hepatitis, 1 JC virus) and 2 in the OBS arm (1 sepsis, 1 JC virus) (both JC virus infections occurred after investigational drugs treatment for progression).

Conclusion: These data indicate that although infections are more common during rituximab maintenance, only a few are severe, and the majority of them can be managed in daily practice.