Phase II trial of reduced dose 90Y Zevalin (0.3 mCi/kg) in patients with mild thrombocytopenia, a Phase III randomized trial of 90Y Zevalin (0.4 mCi/kg) versus a standard course of rituximab (375 mg/m2 weekly x 4), a Phase III nonrandomized trial of 90Y Zevalin (0.4 mCi/kg) in patients with rituximab-refractory follicular NHL, and an expanded access trial in patients with relapsed or refractory NHL. All patients had < 25% bone marrow involvement, ANC > 1500/mm3, platelets > 100K/mm3, and no prior high-dose therapy. These patients are a refractory population with advanced disease: median age 60 yrs (range: 24 ñ 85 yrs); 10% splenomegaly; 42% with bone marrow involvement; 16% intermed/high or high IPI risk groups; 31% with => 4 prior therapies. Overall response rates (ORR) for the two Phase III trials, using the International Workshop response criteria for NHL [JCO 1999;17(4)1244-53], were determined by an independent panel, blinded to investigator assessment of response. The ORR for the randomized trial was 80% (34% CR/CRu) in the Zevalin arm and 56% (20% CR/CRu) in the rituximab arm. The ORR in the nonrandomized, rituximab-refractory trial was 74% (15% CR/CRu). Toxicity was primarily hematologic. Median nadirs: ANC = 800/mm3; platelets = 40K/mm3; and Hgb = 10.3 g/dL. Grade 4 neutropenia and thrombocytopenia occurred in 30% and 10% of patients, respectively. The median duration below an ANC of 1000 cells/mm3 or platelets of 50K/mm3 was 13 days and 14 days, respectively, for all patients, and 22 and 25 days, respectively, for those patients with a Grade 3 or 4 nadir. 7% of patients were hospitalized with infection or febrile neutropenia. Myelodysplasia or AML was reported in 5 patients (1.4%) from 8 to 34 months after Zevalin treatment, which is below the 4-8% cumulative background incidence reported for such heavily-pretreated patients. In summary, Zevalin therapy is effective and well tolerated, even in this refractory population at risk for toxicity.

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Histiocyte-rich, T cell rich B cell lymphoma. A distinct clinicopathological entity

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Background: Although it has proven difficult to delineate diagnostically reproducible and clinically relevant subgroups, the heterogeneity of diffuse large B cell lymphomas (DLBCL) is widely acknowledged. In 1992 we reported on six cases that suggested that histiocyte rich, T cell rich B cell lymphoma (HRTR-BCL) may be identified as a separate clinicopathological entity within DLBCL.

Methods: In a retrospective study of 60 cases, the clinicopathological features of HRTR-BCL were analyzed in order to provide a precise disease definition and to suggest reliable differential diagnostic criteria. In addition the clinical relevance of recognizing HRTR-DLBCl as a distinct lymphoma entity was evaluated and the predictive value of several phenotypic markers in TRHR-BCL was assessed.

Results: HRTR-BCL is easily distinguished from other B cell lymphomas rich in stromal T cells by (1) a diffuse or vaguely nodular growth pattern, (2) the presence of a minority population of CD15-, CD20 large neoplastic B cells, (3) a prominent stromal component composed of both T cells and nonepitheloid histiocytes, and (4) the absence of small reactive B cells. These diagnostic criteria also allow one to differentiate HRTR-BCL from lymphocyte-rich classical Hodgkinzs disease, from lymphocyte-predominant Hodgkinzs disease, paragranuloma type and from peripheral T cell lymphoma. HRTR-BCL typically affects middle-aged male patients who present with advanced-staged disease that is not adequately managed with current therapeutic strategies. Whereas proliferation fraction and p53 overexpression, in addition to the clinical variables incorporated in the IPI, significantly correlated with response to treatment and survival in a univariate analysis, only the IPI score identified relevant prognostic HRTR-BCL subpopulations in a multivariate model.

Conclusion: These results confirm that HRTR-BCL constitutes a morphologically identifiable and clinically distinct diffuse large B cell lymphoma subtype. Based on the morphological aspect and the immunophenotypic profile of the neoplastic B cells, we speculate that HRTR-BCL may be derived from a progenitor cell of germinal centre origin. On the analogy of germinal centre-derived lymphomas in SJL/CD57L mice, reverse immune surveillance phenomena may determine the peculiar histologic features of the disease as well as its aggressive biologic behaviour.

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Gastric MALT lymphomas prospective LY03 randomised cooperative trial: preliminary results of the molecular follow-up

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Purpose: Gastric extranodal marginal zone lymphoma of MALT-type can regress after anti-Helicobacter pylori treatment. The IELSG, the Groupe d'Etude des Lymphomes de l'Adulte (GELA) and the United Kingdom Lymphoma Group (UKLG) have conducted a trial to ascertain whether the addition of chlorambucil is of benefit after anti-H. pylori therapy. At the last interim analysis, 105 patients out of 189 (55%) had achieved a complete histologic remission after antibiotics. In order to further assess the ability of treatment to eradicate the lymphoma clone we analysed the gastric biopsies from a subset of the patients by PCR targeted to the immunoglobulin heavy chain genes, an established molecular marker for molecular residual disease assessment.

Methods: At diagnosis, DNA extracted from paraffin-embedded tumour tissues were first analysed using FR3A primers. Polyclonal cases were analysed with FR2A primer. DNA samples from gastric biopsies performed during the follow-up were analysed for the presence of residual disease. Patient-specific oligonucleotides were designed to increase the specificity and sensitivity of the PCR assay. Results: Fifty-seven cases were analysed at diagnosis. Forty-nine cases were monoclonal by PCR. Forty-six out of the 57 achieved histologic complete remission (hCR): 34 cases underwent molecular follow-up. Ten had not been randomised, thirteen had been randomised to chlorambucil, 11 to observation alone. Fourteen (41%) patients failed to achieve molecular complete remission (mCR), as a whole. At one year after hCR, 17 patients were in mCR and a further 3 were in mCR by 2 years (mCR 59%). After a median follow-up of 2 years (6-57 months), 13 (38%) patients are still in mCR at the last follow-up biopsy. mCR was persistent in 5/6 of patients randomised to chlorambucil, and in 5/9 of the ones randomised to observation alone. However, to date those with persistent molecular disease do not show a higher rate of histologic relapse.

Conclusion: About half of the patients with MALT lymphoma can achieve molecular remission after antibiotic therapy. The presence of molecular disease in the absence of histologic disease, apparently not associated to histologic relapse, could be due to the persistence of lymphoma - related terminal differentiated plasmacells. However, since the indolent nature of MALT lymphomas, a longer follow-up might be needed.

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Consolidation radiotherapy to bulky disease in aggressive non Hodgkin's lymphoma. Results of the NHL B-94 trial of the German high grade NHL study group (DSHNHL)

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Purpose: The role of radiotherapy (RT) in the treatment of high grade NHL ist not very well defined. In the study design of the DSHNHL radiotherapy was added after chemotherapy (CT) in patients with bulky disease. The presented data analyse patients with bulky disease only treated in the NHL B-94 trial.

Methods: Patients with an initial tumor size larger than 7.5 cm were defined to have "bulky disease". An irradiation to the bulk area had to be given after 6 cycles of CT. Total dose was 36 Gy given in single fractions of 1.8-2 Gy 5 times per week. Out of the total of 959 pts.included in the study 323 (33.9%) had bulky disease, 170 of them had additional extranodal lymphoma; therefore, the incidence of bulky disease in patients without extranodal disease was 15.9% (153/959). To evaluate the impact of radiotherapy after chemotherapy, we analysed the group of 366 patients with nodal disease only, who completed therapy according to the protocol. Out of this group 91 pts. had bulky disease, 84 were treated with RT, 7 patients were not irradiated because of prior surgery.