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.

120 ORAL

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.

121 ORAL

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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122 ORAL

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.

Results: Overall relapse rate in the patients group was 71/366 (19,4%). We analysed relapse rates in areas initially involved: out of a total of 1205 analysed areas, 11.4% showed the criteria of bulk, 1068 had lymphomas <7.5 cm. There was no difference in the two groups concerning the relapse rates in the initially involved nodal areas (8.6% (no bulk) vs 8% (bulk). The risk of local recurrence in the irradiated group with bulky disease was as low as in the (unirradiated) group without one. Recurrence free survival rates also showed no difference (77.3% (no bulk) vs 74.1% (bulk)). Regarding the whole group of patients with nodal disease, pts with bulky disease had a significantly shorter time to treatment failure than pts without bulk: three year recurrence free survival was 66.1% (no bulk) vs.53.3% (bulk).

Conclusion: The fact that in irradiated patients the poor prognostic factor "bulky disease" is not significant anymore supports the data from the literature that radiotherapy is an effective consolidation treatment in patients with aggressive NHL.

123 ORAL

Long term follow up of a randomised trial comparing local radiotherapy with wide field radiotherapy in stage I and II Hodgkin's disease

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Introduction: Between 1970 and 1979 a randomised controlled trial of involved field radiotherapy (IFRT) against extended field radiotherapy (EFRT) in patients with stage I and IIA Hodgkin's disease was undertaken by the British National Lymphoma Investigation (BNLI). In patients without B symptoms the comparison was between involved field and either mantle or inverted Y radiotherapy, in patients with B symptoms the comparison was between mantle or inverted Y radiotherapy and total nodal irradiation. With a minimum of 21 year follow up the results have been analysed for relapse-free and overall survival rates. 603 patients were randomised into this trial, median age 30 (range 15 to 78) of whom 363 (60%) were male. 433 (72%) had nodular sclerosing disease, 94 (16%) mixed cellularity, 68 (11%) lymphocyte predominant and 7 (1%) lymphocyte depleted. 220 (37%) had mediastinal involvement.

Results: In laparotomy confirmed stage I and IIA disease (n=332) there is a significant difference in recurrence-free survival between IFRT and EFRT. This difference is maintained across the prognostic groups even in very favourable patients female <40yrs with no mediastinal disease). The actual difference is 12% at 5, 10 and 15 years from initial treatment (p = 0.02). A similar but statistically non-significant difference is seen in the patients having no laparotomy (n=210) and in no group is there any effect between primary radiotherapy treatment and overall survival. In stage I and IIB disease no impact on recurrence-free survival or overall survival was seen between patients having IFRT and EFRT. Limited data on late toxicity in this group of patients shows no difference in rates of second malignancy between patients receiving IFRT and EFRT with an incidence of 13 and 14% respectively.

Conclusion: long term follow up of this trial confirms the recognised increased relapse rate in patients receiving IFRT compared to EFRT for early stage disease but no detrimental impact of IFRT on overall survival or advantage of IFRT in second malignancy rates is seen. The results from radiotherapy alone for patients with B symptoms are poor and justifies current practice using primary combination chemotherapy for these patients.

Head and neck cancer

124 ORAL

Prognostic Significance of COX-2 Expression in Advanced Head and Neck Cancer Treated with Radiotherapy in a Phase III RTOG Trial (90-03)

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Objective: To assess the impact of cyclooxygenase-2 (COX-2) expression on the outcome of patients with advanced head and neck carcinomas (HNC) treated with radiotherapy.

Methods: Unstained histologic slides were available from 154 of 268 analyzable patients randomized to the standard radiation arm of a Phase III RTOG trial (IJROBP 48:7, 2000). The slides were deparaffinized, rehydrated, blocked for endogenous peroxidase, and stained with polyclonal COX-2 antisera (PG-27b, Cayman Chemical). Immunoreactive complexes were detected using the standard ABC method and evaluated utilizing an immunohistochemical (IHC) scoring system for the intensity of staining (0: no, 1: weak, 2: moderate, and 3: strong staining) and the % of tumor cells staining positive (0: none, 1: 1-10%, 2: 11-50%, 3: 51-80%, and 4: 81-100%). These parameters, individually or combined (i.e., product of scores), were correlated with the clinical prognostic features and time to locoregional failure (TTLRF) or distant metastasis (TTDM), which were calculated using cumulative incidence method with testing by Gray's test. The median follow-up was 59.5 months for living patents.

Results: There were no significant differences in the T-stage, N-stage, tumor site, KPS, age, gender, and race or in the therapy outcome between patients with (n=154) and those without (n=114) COX-2 assessment. The frequency distribution by % cells stained was 0: 12, 1: 22, 2: 51, 3: 51, and 4: 12 and by staining intensity was 0: 18, 1: 3, 2: 47, and 3: 86. There was no significant correlation between the TTLRF and COX-2 expression. We found a significant correlation between the TTDM and the staining intensity (p=0.038 for 0-1 vs 2-3), the % of tumor cells stained (p=0.011 for 0-2 vs 3-4), or the combined scores (p=0.016 for 0-1 vs 2-12; p=0.039 for 0-3 vs 4-12).

Conclusion: This study showed that 88% of advanced HNC express COX-2, an enzyme playing a role in carcinogenesis and tumor response to therapy. No correlation was detected between COX-2 expression and the clinical prognostic factors but a there was a significant correlation between COX-2 expression and TTDM, which suggests that COX-2 expression is a useful independent prognostic determinant of distant spread. If confirmed by further study, COX-2 expression can serve as a patient stratification or selection variable for clinical trials addressing new or aggressive adjuvant therapy.

125 ORAL

Hypoxia and hemoglobin as prognostic markers of survival in head & neck carcinoma after primary radiation therapy. An international multi-center study

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Purpose: To assess the prognostic value of pretreatment oxygenation status in head and neck squamous cell carcinoma (HNSCC) after primary radiotherapy.

Methods: Tumor oxygen partial pressure (pO2) was measured by invasive electrodes (Eppendorf) in 321 stages III-IV SCCHN from 6 centers, n=267 male and n=54 female. Median age was 58 years (range 22-92). Nine patients with distant metastases had palliative treatment and 314 patients had a full course of radiation therapy alone or combined with surgery, chemotherapy or hypoxic sensitizer. Endpoints were overall survival (OS) and pO2 parameters were fraction of pO2 values<2.5 mmHg (HF2.5),<5 mmHg (HF5) and median tumor pO2 (mmHg).

Results: Inter-tumor variability was large as the median tumor pO2 ranged from 0 to 77 mmHg (overall median=10 mmHg). Both HF2.5 and HF5 ranged from 0 to 100% (median=20% and 29%, respectively). At 3 years follow up 192 patients were dead. By Kaplan-Meier analysis at 3 years HF2.5 and HF5 were prognostic for OS in all 314 patients (27% vs. 38%, p=0.005 and 31% vs. 35%, p=0.04, respectively) whereas median tumor pO2 was not significant (p=0.30). By multi-variate analysis HF2.5 and stage were significant independent prognostic variables of OS. Hemoglobin (Hb) data were available in 274 patients. Also Hb was a strong prognostic marker for OS (22% vs 39%, p=0.001) when devided by an over all median = 13.2 g/dl. There was no correlation between Hb and HF2.5, HF5 or median pO2, respectively. By multivariate analysis in this subgroup of patients Hb, HF2.5 stage and age were significant prognostic variables of OS.

Conclusions: This study showed that tumor hypoxia defined by HF2.5 adversely affected OS in advanced SCCHN treated by primary radiation therapy. Also, Hb was a strong prognostic marker of OS and apparently independent of HF2.5.