1192 POSTER*

Cardiac lesions after mediastinal irradiation (r) for Hodgkin's disease (HD)

C. Glanzmann[1], Ph. Kaufmann[2,3], R. Jenni[2], O.M. Hess[2]. [1]Department of Radiation Oncology; [2]Department of Nuclear Medicine; [3]Department of Internal Medicine, University Hospital of Zürich, Switzerland

Purpose: Analysis of the risk of cardiac r with a low dose per fraction and an intermediate total dose with or without chemotherapy (c).

Methods: Between 1964 and 1992, 367 patients with HD had curative r with or without c including the mediastine. The mean length of follow up is 11 2 years with a range between 1 and 32 years. 97% of the patients have a complete follow up and 155 (64% of the living patients) consented in a special heart examination including: rest and exercise ECG, echocardiography and myocardial perfusion scintigraphy. Risk factors were also evaluated: body mass index, blood pressure, smoking history, diabetes mellitus, cholesterolemia and cardiac disease before r. In 97% of the patients, the dose per fraction in the anterior heart was between 1.3 and 2.1 Gray with a total dose between 30 and 42 Gray.

Results: The risk of fatal cardiac ischemic events (mi) and/or a sudden unexpected death (sd) was significantly higher than expected with a relative risk of 4.2 for mi and 6.7 for mi or sd. The actuarial incidence of fatal or non fatal ischemic cardiac events or of sd or of congestive heart failure was 3.6% after 10 years, 12.9% after 20 years and 41.7% after 30 years. In the patients without risk factors this incidence was 1.3% after 10, 20 and 30 years, not significantly different from the expected value. In patients without risk factors and without c there was no ischemic or other cardiac event. Actuarial incidence of valvular thickenings after 30 years was 60%, mostly without hemodynamic disturbance. C including adriamycin was not a risk factor for cardiac events.

Conclusion: After r of the heart with a low dose per fraction and an intermediate total dose, the incidence of major ischemic cardiac events is significantly higher than expected. But in patients without other cardiovascular risk factors, this risk seems low. C including adriamycin with a total dose between 150 and 300 mg/m2 did not increase this risk. Valvular thickenings are frequent but mostly without hemodynamic disturbance.

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Clinical factors predictive of the probability of upstaging patients with clinical stage (CS) I or II supradiaphragmatic Hodgkin's disease (HD) to pathological stage (PS) III_2 or IV by staging laparotomy

G. Aragón[1], C.A. Regueiro[1], M. Martín[1], I. Millán[2], J. Romero[1], A. de la Torre[1], E. Polo[1], C. Sanz[1], F.J. Valcárcel[1]. [1]Department of Radiation Oncology; [2]Dept. of Biostatistics, Clinica Puerta de Hierro, Madrid, Spain

Background: Some studies have shown that certain clinical factors predict the probability of abdominal involvement in patients with CS I and II disease. The identification of the clinical factors that predict the probability of upstaging patients with CS I or II to PS III_2 or IV would be useful for treatment selection since these patients would be at high risk of relapse following radiotherapy alone.

Patients and Methods: We reviewed the results of surgical staging in the 361 consecutive patients with CS I or II Hodgkin's disease admitted at our department between 1970 and 1985, all of whom underwent staging laparotomy. We performed a multivariate analysis to identify the clinical factors predictive of the probability of upstaging those patients to PS III_2 or IV.

Results: Out of 361 patients, 39 were upstaged to PS III_2 or IV The three factors found to significantly influence the probability of upstaging to PS III_2 or IV were fever [present *vs* absent: relative risk (RR): 9.68; 95% confidence interval of the relative risk (95% CI): 4.44–21.11; $P < 0.0001$], number of involved nodal sites [≤ 4 *vs* >4 sites: RR: 8.17; 95% CI: 2.51–26.56; $P < 0.001$] and mediastinal involvement [normal mediastinum *vs* nonbulky mediastinal disease: RR: 0.24; 95% CI: 0.08–0.70; $P < 0.01$ and normal mediastinum *vs* bulky mediastinal disease: RR: 0.25; 95% CI: 0.09–0.68; $P < 0.01$]. According to these results, the predicted probability of upstaging a patient with a number of involved sites ≤ 4 and no fever to PS III_2 or IV was lower than 10%.

Conclusions: The results of this analysis suggest that certain clinical factors are useful to identify those patients with high and low risk of having extensive abdominal nodal or extranodal disease disclosed by surgical staging.

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Intermediate-high dose sequential single agent chemotherapy combined with irradiation in advanced Hodgkin's disease (HD)

V. Bonfante, G. Bonadonna, A. Santoro, S. Viviani, L. Devizzi, H. Soto Parra, M. Zanini, A. Di Russo, F. Villani, P. Valagussa. Istituto Nazionale Tumori, Milan, Italy

To improve results, in March 1993 we started a pilot study delivering chemotherapy at dose-size and dose-intensity (DI) higher than current regimens, with G-CSF support combined with involved-field radiotherapy (IF-RT). The program utilized cyclic administration of the most effective drugs in HD given sequentially. Epidoxorubicin (EPI), 140 mg/sqm plus vincristine 1.4 mg/sqm day 1 and prednisone 50 mg/sqm day 1–5 was followed by cyclophosphamide (CTX) 4000 mg/sqm on day 15 and by etoposide (VP-16) 2000 mg/sqm on day 29. After a two week interval, the same sequence was recycled once and a final EPI was given on day 85. Four weeks after, IF-RT (30–36 Gy) was started. G-CSF was given from day 6 to 11 after EPI and CTX and from day 3 to 11 after VP16. Fifty untreated consecutive pts, entered as of 1/96, are evaluable. Characteristics were: M/F 23/27; median age 30 yrs (range 17–54); stage IIB 27; III 9; IV 14; B symptoms 43; bulky disease 19; <3/>3 sites 12/38.

After a median follow-up of 27 mos the results were as follows: complete remission (CR) 94%; freedom from progression 72%; overall survival 96%.

Compliance was good; pts completed the drug program within a median of 12.6 weeks and the median DI was 0.95. No cardiac or lung toxicity was detected. Two leukemias developed at 20 and 22 mos. This program was safe and able to induce a high CR rate. However, the percent of pts in continuous CR is superimposable to that achieved with conventional combinations. For this reason the risk/benefit ratio of this intensive regimen seems to be higher compared to standard treatments.

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FISH identifies different types of duplications with 12q13–15 as the commonly involved segment in B-cell lymphoproliferative malignancies characterized by partial trisomy 12

J. Dierlamm[1], I. Wlodarska[1], L. Michaux[1], J.R. Vermeesch[1], P. Meeus[1], G. Verhoef[2], J. Thomas[3], C. Mecucci[4], A. Hagemeijer[1], H. Van den Berghe[1]. [1]Center for Human Genetics and Flanders Institute of Biotechnology, the Departments of [2]Hematology; [3]Oncology, University of Leuven, Belgium; [4]Hematology and Bone Marrow Transplantation Unit, University of Perugia, Italy

Partial trisomy 12 was detected in 18 out of 1836 cytogenetically analyzed cases of B-cell NHL and occurred predominantly in clinically progressive chronic lymphocytic leukemia, mixed cell type, and advanced stage follicle center cell lymphoma (FCCL) at the time of relapse or transformation into diffuse large cell lymphoma (DLCL). Partial trisomy 12 consistently included the long arm of chromosome 12, either completely or partially, and resulted from dup(12)(q) or different other rearrangements involving chromosome 12. The duplications were cytogenetically identified as dup(12)(q13q23), dup(12)(q13q22), or dup(12)(q13q15) in FCCL or t(14;18)-positive DLCL; dup(12)(q13q22) or dup(12)(q13q24) in chronic lymphocytic leukemia; and dup(12)(q13q21) in a case of t(14;18)-negative DLCL. FISH using library probes and a panel of YAC probes mapped along the long arm of chromosome 12 confirmed the cytogenetic results in all cases analyzed except for three cases of t(14;18)-positive FCCL or DLCL with dup(12)(q). In these cases, FISH showed similar, possibly identical duplications, which involved a region more centromeric (12q11–q21) than assumed by karyotypic analysis (12q13–22 or 12q13–23). In addition, commonly duplicated regions of chromosome 12 could be defined: 12q11–21 for FCCL or t(14;18)-positive DLCL, 12q13–22 for chronic lymphocytic leukemia, and 12p13–q15 for marginal zone cell lymphoma, all of which overlapped in 12q13–15.

1196 POSTER

Clinico-pathological study of the adult Hodgkin's disease. 15-year experience, National Cancer Institute, Cairo, Egypt

M. Saber, I. El-Attar[1], M. El-Mongi[2], N. Gad El-Mawla, M.R. Hamza[1]. Department of Medical Oncology, [1]Medical Biostatistic; [2]Radiotherapy, NCI, Cairo University, Egypt

Purpose: This is a 15-year retrospective study of the histologic and clinical

features as well as response to treatment and survival of adult Hodgkin's disease (HD) patients.

Methods: The study was performed on patients presented to NCI, Cairo, during the period from January 1975 to December, 1991.

Results: The total number of patients included was 914. Seventy percent (No. 642) were males, male to female ration 2.4:1 and the median age was 31 years. The most common histologic subtype was mixed cellularity (47.9%) followed by nodular sclerosis (21.7%), lymphocyte predominance (18%) and lymphocyte depletion (12.3%). Fifty seven percent stage III and IV and 5% presented with relapsing disease. Nodal presentation was encountered in 92%, and B symptoms was found in 41% of cases. Early stages were treated mainly by radiotherapy with complete response (CR) in 99% for stage I, 88% for stage II and 86% for stage III. patients with stage III and IV treated with combination chemotherapy achieved CR in 78.6% and 53.1% respectively. The 5-year relapse free survival (RFS) and overall survival (OS) were 35% and 43.7 while 10-year RFS and OS were 3% and 4.6% respectively.

Conclusion: These poor results may imply that we may have been less aggressive in our treatment or we are dealing with a population of patient with immune derangement due to poor nutrition or chronic parasitic infestation. Also endemicity of Bilharziasis in Egypt with liver affection may limit administration of optimal doses and schedules of chemotherapy.

1197 POSTER

Somatostatin receptor scintigraphy for the initial staging of non-Hodgkin's lymphomas

P.J. van den Anker-Lugtenburg, B. Löwenberg, S.W.J. Lamberts, H.Y. Oei, R. Valkema, E.P. Krenning. *Erasmus University and University Hospital Rotterdam; Dr. Daniel den Hoed Cancer Center, Rotterdam, The Netherlands*

Purpose: We present the results of a prospective blinded study comparing somatostatin receptor (SS-R) scintigraphy with conventional staging methods for initial staging of patients with NHL.

Methods: 150 Consecutive previously untreated NHL patients (50 low grade, 66 intermediate grade, 28 high grade and 6 unclassifiable) underwent scintigraphy after i.v. injection of [111-In-DTPA-D-Phe-1]-octreotide, 220 MBq. SS-R scintigraphy and conventional diagnostic tests were interpreted independently and the results compared.

Results: 89% (133/150) of the patients had a positive scan. In 31 patients (21%) the clinical stage was altered because of the result of SS-R scintigraphy and as a result the treatment plan was changed in 5 patients (3%). The lesion-based analysis showed an overall sensitivity of 65% (288/443). The sensitivity in the supra-diaphragmatic region was 72% (189/261) and 50% (70/139) in the infra-diaphragmatic region. A false positive uptake of radioactivity was observed in 16 lesions, mainly due to scars, hematomas and infections.

Conclusion: SS-R scintigraphy appears to disclose unknown lymphoma localizations in some patients with NHL, however the sensitivity especially for infra-diaphragmatic lesions is low.

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Analysis of genomic instability by microsatellite analysis in childhood Burkitt's and large cell diffuse lymphoma

L.M. Ball, C. Riddell, C. Tatlidil, S. Murray, K. Samson, C.L. Lannon, K. Laybolt, M. Henry, A. MacKay, J. Mu, D. van Velzen. *Departments of Molecular Genetics, Quantitative Pathology and Image Analysis, Haemato-Oncology, IWK/Grace Health Centre, Halifax, Nova Scotia, Canada*

Purpose: Genomic instability may, in addition to having bearing on the propensity for developing malignancy, be of relevance to sensitivity to genome directed therapy. In childhood lymphoma, highly variable karyotype abnormalities are commonly reported, while chemotherapy in view of disease localisation and stage at presentation is often the only viable option. For both aspects, information on prevalence of this abnormality in lymphoma is of interest.

Methods: Primary diagnostic, consecutive samples of 16 cases of diffuse large cell lymphoma (9 T-cell, 7 B-cell, mean age 9 y 9 m (range 1 y 5 m–16 y 8 m) and 13 Burkitt's Lymphoma, mean age 8 y 3 m (range 4 y 2 m–14 y) seen in a single treatment centre between 1976 and 1996 were included in the study. After routine extraction, amplifications were carried out at the loci D3S1304 and D3S1537 (both closely distal to the VHL tumour suppressor gene), ELN gene, D7S1870, IFNA, D1S243 (1p36) all of which show microsatellite variation. Analysis used isotopic labelling during amplification followed by non-denaturing gel electrophoresis and autoradiography.

Results: In two cases: Male age: 9 yrs 7 m, abdominal mass, B-cell large cell diffuse MNHL and Male, age 5 yrs, caecal mass, Burkitt's Lymphoma, unusual variants were observed. Other lesions were normal, although no normal tissue was available from separate analysis for direct comparison.

Conclusions: Only 2/28 childhood Burkitt's/large cell diffuse MNHL feature minor microsatellite variations warranting further study but suggesting a minor role for this pathway in contributing to genomic instability in lesions of this type.

1199 POSTER

Primary gastric lymphoma – The Royal Marsden Hospital experience

R.A. Popescu[1], A. Wotherspoon[2], D. Cunningham[1], M. Hill[1], S. Milan[1], J. Prendeville[1]. *The Royal Marsden NHS Trust, Sutton, Surrey, Departments of [1]Medicine; [2]Histopathology, London, UK*

Purpose: We aimed to determine the role of surgery in the treatment of primary gastric lymphoma (PGL) in patients receiving chemotherapy (CH) at this hospital since 1985.

Methods: Patients with intermediate- or high-grade PGL, defined according to the criteria of Lewin and Herrmann, and staged according to Musshoff, were identified using a prospectively accrued database.

Results: 41 patients (29 men, average age 65 (range 19–81), median follow up 4 1/4 years) fulfilled the inclusion criteria. At presentation, 35 patients complained of anorexia, 33 of abdominal discomfort, 31 of weight loss and 11 of recurrent vomiting. 15 patients had GI bleeding (5 haematemesis, 5 melaena and 5 microcytic anaemia), and 5 patients presented with perforation, 3 requiring emergency SX. 17 patients had early PGL (9 stage IE, 8 stage IIE1). 8 of 17 patients had initial SX, and 2 relapsed (1 before CH could be initiated). One of 9 patients receiving CH alone relapsed. All 3 relapsing patients achieved remission with further CH. Of the patients with more advanced stage PGL, 16 received CH alone, 5 SX followed by CH and 3 had radiotherapy (RT) as well as CH. The group receiving CH had more patients with advanced disease. In total 6 patients died with disease, all with advanced stage: 3 had received CH alone, 2 SX + CH and 1 CH followed by RT. All 6 deaths occurred within 18 months of diagnosis. 3 patients had malabsorption following gastrectomy, while GI-bleeding occurred in 5 patients following chemotherapy (none severe). No perforations occurred in the 25 CH patients.

Conclusions: CH alone appears to be as efficient as the combination of SX and CH in intermediate and high-grade PGL of any stage. Complications rarely occurred as a side-effect of CH, and were not life threatening.

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Inhibition of spontaneous apoptotic cell death of B-chronic lymphocytic leukemia (B-CLL) cells by interleukin-12 in vitro

S. Duensing, S. Schuhknecht, A. Franzke, J. Buer, M. Probst-Kepper, R. Hoffmann, A. Ganser, J. Atzpodien. *Department of Hematology and Oncology, Medizinische Hochschule Hannover D-30623 Hannover, Germany*

A variety of cytokines including interleukin-2 (IL-2) have been reported to modulate cell survival in B-CLL. Since functional similarities between IL-2 and IL-12 have been described, we analyzed potential effects of IL-12 on the spontaneous vitro apoptosis of B-CLL cells. Ten peripheral blood samples enriched for B lymphocytes from seven patients with B-CLL (three men and four women aged 44 to 76 years) who had received no specific antineoplastic therapy including steroids for at least 6 months prior to sample collection were analyzed. One patient presented with stage 0 (according to the Rai staging system), four patients were stage II, and two patients stage IV. Mean time interval from first diagnosis to sample collection was 60 months. Peripheral blood mononuclear cells were isolated and depleted of contaminating cells via plastic adherence and sheep red blood cell rosetting. Cells were then short term cultured for 24 hours under serum free conditions in the presence of IL-12 (1 ng/ml). Incubation with IL-4 (10 ng/ml over 24 hours), which has been reported to effectively suppress spontaneous apoptosis in vitro was used as control for potential inhibitory cytokine effects. Apoptotic cell death was measured employing an enzyme-linked immunoassay measuring cytoplasmatic histone-associated fragmented DNA mono- and oligonucleosomes via anti-histone antibodies (Boehringer Mannheim, Germany). Results of the photometric absorbance (A) measurements are given as ratio of $A_{\text{cytokine mediated apoptosis}}/A_{\text{spontaneous apoptosis}}$ (A_{cy}/A_{sp}). We found that IL-4 used as control could induce inhibition of apoptotic cell death (as